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The Course of Cognitive Impairment across the Psychosis Spectrum

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The Course of Cognitive Impairment across the Psychosis Spectrum

**Josephine Mollon
PhD**

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Preface

This thesis is a ‘*Thesis incorporating publications*’. The second chapter comprises a published journal article of which I am the first author (Mollon et al., 2015). This chapter is preceded and followed by additional comments. The published supplemental materials are presented in the Appendix section.

Statement of Contribution

This document was written as a doctoral thesis by myself, Josephine Mollon.

Chapter 2 of this thesis forms a jointly authored publication, which was published in JAMA Psychiatry with the title '*Psychotic Experiences and Neuropsychological Functioning in a Population-based Sample*' by Josephine Mollon (myself), Anthony David (supervisor), Craig Morgan, Souci Frissa, David Glahn, Izabela Pilecka, Matthew Hotopf and Abraham Reichenberg (supervisor). I carried out the literature search, conducted data analyses, interpreted results, drafted and submitted the manuscript and subsequent revisions, and acted as corresponding author.

Supervisors and collaborators gave guidance on chapter 3 and I completed all analysis of data and writing. Advice was given on chapter 4 by supervisors and I conducted all data analyses and completed writing. Supervisors advised on the introduction and discussion chapters and I completed all writing.

Abstract

The majority of schizophrenia patients exhibit significant, diffuse cognitive impairment. Understanding the course and nature of this impairment is essential to elucidating etiology and treatment. Previous studies have been unable to trace the course of cognition from infancy to adulthood and assess true developmental change. Cognitive deficits in individuals with subclinical psychotic experiences may provide important clues about clinical psychotic disorders. Yet, developmental change and the effects of age, sociodemographic and familial factors have not been examined. Moreover, while there is evidence for connection abnormalities in the brains of schizophrenia patients, little is known about the structure of cognitive functioning across the psychosis spectrum i.e. in subclinical psychotic experiences and clinical psychotic disorders.

The first study examined the association between subclinical psychotic experiences and cognitive functioning in a general population sample. Adults with psychotic experiences showed significant verbal and memory, but not processing speed deficits. Only older adults with psychotic experiences showed medium to large verbal and memory deficits when adjusting for sociodemographic factors, psychiatric morbidity and cannabis use. First-degree relatives showed a significant verbal, but not memory impairment.

The second and third studies used data from a longitudinal cohort to examine 1) the course of cognitive functioning from infancy to adulthood and 2) cognitive network structure in childhood and adulthood. Individuals with depression, psychotic experiences, affective psychotic disorder and non-affective psychotic disorder were compared to controls. Affective psychotic disorder, psychotic experiences and depression groups showed a degree of cognitive impairment across infancy and adulthood, but only those with non-affective psychosis showed large, progressive

deficits across multiple domains. Individuals with non-affective, affective and subclinical psychosis also showed qualitative and quantitative abnormalities in cognitive network structure, with the two clinical groups showing larger, widespread anomalies. Controls showed increasing reliance on working memory between childhood and adulthood, while all other groups remained reliant on low-level cognitive processes.

Altogether, these findings suggest that the course of cognitive impairment differs across the psychosis spectrum. Despite distinct profiles of impairment, abnormalities in cognitive network structure were seen across the spectrum, highlighting the importance of looking beyond cognitive deficits to how performance is achieved.

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Introduction

Cognition in Schizophrenia

Schizophrenia is a severe and disabling psychiatric disorder characterized by positive psychotic symptoms, such as hallucinations and delusions, and negative symptoms, such as impoverished emotional expression and avolition. The majority of schizophrenia patients also exhibit significant, diffuse cognitive impairment (Reichenberg and Harvey, 2007; Heinrichs and Zakzanis, 1998). Early theories viewed this impairment as secondary to the positive and negative symptoms i.e. as a result of cognitive intrusion and poor engagement (Palmer et al., 2009). Since then, however, cognitive dysfunction has been established as a core feature of schizophrenia spectrum and other psychotic disorders (APA, 2013).

An extensive literature documenting the cognitive profile of schizophrenia patients provides evidence of a large, general deficit equal to one standard deviation, or 15 IQ points, below controls (Reichenberg and Harvey, 2007). Low IQ has been reliably replicated as a risk factor for schizophrenia (Aylward et al., 1984; Touloupoulou et al., 2006; David et al., 1997). Specific deficits across multiple cognitive domains are also well established, with the largest effect sizes reported to be in memory, executive function and processing speed domains (Heinrichs and Zakzanis, 1998; Fioravanti et al., 2005; Dickinson et al., 2007).

Establishing effective treatments for cognitive dysfunction has proved challenging. Despite candidate pharmacological mechanisms (Harvey, 2013) and promising behavioural treatments (Wykes et al., 2011) none has received regulatory approval. Moreover, remitted schizophrenia patients may report better social functioning and

quality of life and yet their cognitive functioning remains as impaired as in non-remitted patients (Brissos et al., 2011). The functional consequences of cognitive deficits are severe and have even been reported to exceed those of the positive and negative symptoms of schizophrenia. Composite measures of cognition have been reported to explain as much as 60% of the variance in functional outcomes, such as occupational functioning and independent living (Green et al., 2000). Similar findings have been reported in early psychosis, with global cognition, as well as specific abilities in reasoning, language and memory, most consistently predicting functional outcome (Allott et al., 2011).

The neurocognitive profile of first episode patients is reported to be similar to that of chronic patients, with meta-analytic findings of medium to large deficits in general cognitive ability, processing speed, attention and memory (Mesholam-Gately et al., 2009). Since effect sizes in first episode patients are comparable to those of chronic schizophrenia patients (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007), these findings, altogether, suggest that cognitive impairment is already apparent during the initial phases of illness and remains relatively stable thereafter.

Overall, schizophrenia patients show substantial cognitive deficits across domains (Reichenberg and Harvey, 2007; Heinrichs and Zakzanis, 1998; Fioravanti et al., 2005; Dickinson et al., 2007), which respond poorly to antipsychotic medication (Keefe and Harvey, 2012), endure despite remission (Brissos et al., 2011) and predict a multitude of functional outcomes (Green et al., 2000). Understanding the course and nature of these deficits is therefore essential to elucidating etiological pathways and treatment mechanisms.

Cognition before Psychosis Onset

Studies in schizophrenia patients are susceptible to confounding by several factors, such as illness chronicity and duration, medication and substance use. Recognition of these methodological limitations, combined with initiatives for early detection and prevention in psychiatry, has led to a surge in research on cognitive functioning prior to illness onset i.e. in individuals at high-risk for psychosis (Brewer et al., 2006; Addington and Barbato, 2012; Agnew-Blais and Seidman, 2013) and during the premorbid stages in individuals who go on to develop a psychotic disorder (Khandaker et al., 2011; Woodberry et al., 2008).

Studies in high-risk samples generally fall under two categories, the first utilizing individuals with attenuated, psychosis-like symptoms i.e. clinical high-risk, and the second utilizing family members of individuals with psychosis i.e. genetic high-risk. Cognitive performance in clinical high-risk groups has been reported to be intermediate to controls and patients, with a general deficit equal to around six IQ points (Bora et al., 2014). Small to medium deficits in specific domains, such as processing speed, working memory and attention have also been replicated (Bora et al., 2014), albeit less consistently (Brewer et al., 2006; Addington and Barbato, 2012). Similarly, a general deficit equal to around 12 IQ points has been reported in young relatives of schizophrenia patients (Agnew-Blais and Seidman, 2013; Bora et al., 2014), with small to medium impairments also reported across numerous specific cognitive domains (Snitz et al., 2006; Agnew-Blais and Seidman, 2013; Bora et al., 2014). In terms of premorbid functioning, retrospective studies of individuals with established psychosis have revealed medium IQ deficits years before illness onset (Khandaker et al., 2011; Woodberry et al., 2008). Relatively little is known about premorbid deficits in specific

cognitive domains, with findings of impaired verbal, working memory and processing speed abilities (Seidman et al., 2006; Cannon et al., 2002; Caspi, 2003).

Overall, cross-sectional findings suggest that cognitive deficits emerge years before illness onset (Woodberry et al., 2008; Khandaker et al., 2011), reach their peak around the first episode (Mesholam-Gately et al., 2009) and remain relatively stable thereafter (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007). Moreover, small to medium premorbid deficits (Woodberry et al., 2008; Khandaker et al., 2011) and medium to large deficits during early and late phases of illness (Mesholam-Gately et al., 2009; Heinrichs and Zakzanis, 1998) support the hypothesis of cognitive decline preceding, and perhaps precipitating, psychosis.

Evidence of an increasing deficit between childhood and adolescence has come from retrospective studies of scholastic ability in future schizophrenia patients (Bilder et al., 2006; Fuller et al., 2002). However, these studies have considerable limitations. First, retrospective studies do not allow for specific hypothesis testing (Brewer et al., 2006). Second, the samples used may not be representative (Reichenberg et al., 2010). Finally, academic performance may be more indicative of personality traits, such as self-discipline, than cognitive functioning (Duckworth and Seligman, 2005).

Prospective, longitudinal data at ages 7, 9, 11 and 13 from the Dunedin cohort has provided evidence for static and dynamic cognitive developmental trajectories in individuals who later developed schizophrenia. Verbal deficits emerged early and remained stable, while deficits in executive function emerged gradually with increasing age (Reichenberg et al., 2010). The authors subsequently used data collected in the same cohort at age 38 to extend these findings. Verbal deficits remained stable beyond childhood into middle adulthood, while deficits in executive function continued to

enlarge with increasing age (Meier et al., 2013). Longitudinal data from Swedish cohorts has also provided evidence for cognitive decline, particularly in verbal functions, between the ages of 13 and 18 (MacCabe et al., 2013). A meta-analysis of population-based studies of premorbid intelligence and schizophrenia, on the other hand, failed to find evidence for an increasing IQ deficit prior to illness onset (Khandaker et al., 2011).

While there is longitudinal evidence for cognitive decline preceding the onset of psychosis, previous studies have not been able to comprehensively chart cognitive functioning from childhood to adulthood. Separate studies have examined the developmental periods encompassing early childhood (Agnew-Blais et al., 2015), late childhood (Reichenberg et al., 2010) and early adolescence (MacCabe et al., 2013), with mixed results (Agnew-Blais et al., 2015). Prospective, longitudinal data from infancy, through childhood and adolescence, to early stages of psychotic illness are needed to fully characterize the course of cognitive deficits.

Psychotic Experiences in the General Population

Psychotic symptoms are increasingly viewed as an extended phenotype in the general population rather than solely as a feature of clinical psychotic disorders (van Os and Reininghaus, 2016). Subclinical psychotic symptoms, or psychotic experiences, have an estimated lifetime prevalence of 5.8% worldwide (McGrath et al., 2015). Psychotic experiences share numerous risk factors with psychotic disorders, such as low IQ, childhood maltreatment and stressful life events (Polanczyk et al., 2010; Johns et al., 2004). Imaging studies also report pathophysiological overlaps between subclinical psychotic experiences and clinical psychotic disorders, including hypofrontality, frontotemporal dysconnection and deficits in grey and white matter (Jacobson et al., 2010; Drake et al., 2015; O'Hanlon et al., 2015). Importantly, psychotic

experiences in early life are associated with increased risk for later psychotic illness (Poulton et al., 2000; Welham et al., 2009) and in adulthood with later hospitalization for psychotic disorder (Werbeloff et al., 2012). Examining psychotic experiences in the general population may therefore be informative for research into the aetiology of psychotic disorders, such as schizophrenia, while avoiding confounding by chronicity, medication and substance use.

Lending support to this hypothesised extended phenotype is evidence that the cognitive profile associated with psychotic experiences bears similarities to that of first episode and chronic schizophrenia patients. There have been several reports of a medium IQ deficit (Horwood et al., 2008; Polanczyk et al., 2010; Kremen et al., 1998), as well as specific small to medium deficits in working memory and processing speed functions (Gur et al., 2014; Kelleher et al., 2012a; Niarchou et al., 2013) in individuals with psychotic experiences. However, previous studies have mostly used young adolescent (Kelleher et al., 2012a; Niarchou et al., 2013) or older adult samples (Ostling et al., 2004; Henderson et al., 1998) and the few studies spanning adulthood have used single measures of cognitive functioning (Johns et al., 2004; Simons et al., 2007). Additionally, heterogeneity in the design and findings of previous studies renders drawing firm conclusions about the nature and size of cognitive deficits difficult.

Psychotic experiences have also been shown to increase risk for non-psychotic psychopathology (Fisher et al., 2013; Rössler et al., 2011; McGrath et al., 2016), although there is evidence that this association is bidirectional in nature, with psychiatric illness also preceding the onset of psychotic experiences (McGrath et al., 2016). Even in the absence of any clinical diagnosis, psychotic experiences have been shown to have severe functional and health consequences, with reports of poorer global functioning (Kelleher et al., 2015), as well as increased self-injury (Honings et al.,

2016), suicidal behaviors (DeVylder et al., 2015; Kelleher et al., 2012b) and mortality (Sharifi et al., 2015). Studies examining psychotic experiences and their functional correlates, therefore, appear to be a worthwhile endeavour.

Conclusions and Aims

There is evidence for cognitive decline preceding the onset of psychotic illness, but longitudinal data from childhood to adulthood are needed to fully characterize the developmental course of cognition across the psychosis spectrum i.e. in individuals with clinical psychotic disorder, as well as subclinical psychotic experiences. Large, representative, epidemiological samples are also needed to fully characterize the general and specific cognitive deficits associated with psychotic experiences across the life course. The aim of this thesis is to examine the course of cognitive impairment across the psychosis spectrum. First, I examined subclinical psychotic experiences and cognitive functioning in adults from an ethnically and sociodemographically diverse general population. The effects of 1) important confounders, 2) age, and 3) familial factors on this association were also examined. Second, I examined IQ change from infancy (18 months) to early adulthood (20 years) using an on-going population representative longitudinal cohort. Developmental change in specific functions during the period encompassing adolescence (from age 8 to 20) was also examined. Individuals with non-affective psychotic disorder, affective psychotic disorder, psychotic experiences and depression were compared to controls. Third, I used data from the same longitudinal cohort to comprehensively examine the structure of cognitive functioning in childhood (age 8), as well as changes in structure between childhood and adulthood (age 20) in the same groups of individuals.

Cognitive Functioning and Subclinical Psychotic Experiences

This chapter comprises the manuscript published online on December 30, 2015, in JAMA Psychiatry with the title '*Psychotic Experiences and Neuropsychological Functioning in a Population-based Sample*'.

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Please note that this chapter differs only slightly from the published manuscript:

- The tables are in a different format than in the published article. The figures are in the published format.
- Single words may differ from the published article.

Psychotic Experiences and Neuropsychological Functioning in a Population Sample

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Abstract

Importance Psychotic experiences in early life are associated with neuropsychological impairment and the risk for later psychopathology. Psychotic experiences are also prevalent in adults, but neuropsychological investigations spanning adulthood are limited and confounding factors have not been examined rigorously.

Objective To characterize neuropsychological functioning in adults with psychotic experiences while adjusting for important socio-demographic characteristics and familial factors, and investigating the effect of age.

Design, Setting and Participants The South East London Community Health (SELCoH) study is a population-based household survey of physical and mental health in individuals 16 years or older conducted from June 1, 2008 to December 31, 2010, in two London boroughs. The study included 1698 participants from 1075 households. Data were analysed from May 6 2014 to April 22, 2015.

Exposures Psychotic experiences measured using the Psychosis Screening Questionnaire.

Main outcomes and measures Neuropsychological functioning measured using tests assessing verbal knowledge (Wechsler Test of Adult Reading), working memory (Spatial Delayed Response Task), memory (Visual Object Learning Task) and processing speed (digit symbol coding task). A composite IQ score of general cognitive ability was calculated.

Results A total of 1677 participants with a mean (SD) age of 40 (17) were included in the analysis. Compared to the group without psychotic experiences, the 171 (9.7%) adults with psychotic experiences did not show a statistically significant impairment on

mean [SD] measures of IQ (95.25 [16.58] vs 100.45 [14.77]; Cohen $d=-0.22$, $p=0.06$) or processing speed (40.63 [13.06] vs 42.17 [13.79], Cohen $d=-0.03$, $p=0.73$), but were impaired on measures of verbal knowledge (31.36 [15.78] vs 38.83 [12.64]; Cohen $d=-0.37$, $p=0.003$), working-memory (20.97 [4.12] vs 22.51 [3.26]; Cohen $d=-0.34$, $p=.005$) and memory (43.80 [8.45] vs 46.53 [7.06]; Cohen $d=-0.28$, $p=.01$). Only participants aged 50 years and older with psychotic experiences showed medium to large impairments in neuropsychological functioning (mean [SD]) on measures of IQ (81.22 [15.97] vs 91.28 [14.31]; Cohen $d=-0.70$), verbal knowledge (28.31 [13.83] vs 38.51 [11.50]; Cohen $d=-0.88$), working memory (19.11 [4.77] vs 21.99 [3.42]; Cohen $d=-0.82$), and memory (39.17 [8.23] vs 44.09 [6.51]; Cohen $d=-0.45$) after adjusting for socioeconomic status, cannabis use, and common mental disorders. Medium impairments (mean [SD]) on measures of working memory (21.27 [3.64] vs 22.62 [2.97]; Cohen $d=-0.45$) and memory (44.32 [5.84] vs 46.91 [5.74]; Cohen $d=-0.45$) were seen in those aged 35 to 49 years and on a measure of verbal knowledge (30.81 [14.17] vs 37.60 [10.48]; Cohen $d=-0.62$) in those aged 16 to 24 years. First-degree relatives of adults with psychotic experiences showed a small impairment on a measure of verbal knowledge (34.71 [12.10] vs 38.63 [10.97]; Cohen $d=-0.36$; $P = .02$), and unrelated cohabitants showed no neuropsychological impairment.

Conclusions and relevance The profile of cognitive impairment in adults with psychotic experiences differed to that seen in adults with psychotic disorders, suggesting important differences between subclinical and clinical psychosis.

Introduction

Schizophrenia has a lifetime prevalence of approximately 1% and combined psychotic disorders of approximately 3% (McGrath et al., 2008; Perälä et al., 2007). A substantial minority of the general population also reports subclinical psychotic experiences, with the World Health Organization World Mental Health Surveys (McGrath et al., 2015) reporting a lifetime prevalence of 5.8% worldwide and of 6.8%, 7.2% and 3.2% in high, middle and low-income countries, respectively. Evidence suggests that subclinical psychotic experiences may lie on a continuum with clinically significant psychotic symptoms and therefore be informative for research into the cause of psychotic illness.

First, psychotic experiences and psychotic disorders share risk factors, including low IQ, childhood maltreatment and stressful life events (Polanczyk et al., 2010; Johns et al., 2004). Second, imaging studies report pathophysiologic overlaps between subclinical and clinical psychosis, including hypofrontality, frontotemporal disconnection and deficits in grey and white matter (Jacobson et al., 2010; Drakesmith et al., 2015; O'Hanlon et al., 2015). Finally, psychotic experiences in early life are associated with an increased risk for later psychotic illness (Poulton et al., 2000; Welham et al., 2009) and in adulthood with later hospitalization for psychotic disorder (Werbeloff et al., 2012). However, psychotic experiences are also associated with nonpsychotic psychiatric disorders, including anxiety, depression (Fisher et al., 2013; Varghese et al., 2009) and suicidal thoughts and behaviour (Nishida et al., 2010; Kelleher et al., 2014).

Lending support to this hypothesized psychosis continuum are the small neuropsychological impairments seen in people with psychotic experiences (**Table 2.1** and **Appendix I, eMethods & eFigure 1** report results of a meta-analysis of previous population studies of neuropsychological functioning and psychotic experiences

(Polanczyk et al., 2010; Johns et al., 2004; Kremen et al., 1998; Horwood et al., 2008; Cannon et al., 2002; Niarchou et al., 2013; Kelleher et al., 2012a; Barnett et al., 2012; Gur et al., 2014; Henderson et al., 1998; Ostling et al., 2004; Dunn and Dunn, 1997; Terman and Merrill, 1960; Wechsler, 1949; Wechsler, 1974; Wechsler, 1991; Wechsler, 1989; Wilkinson and Robertson, 2006; Gur et al., 2010; Heim, 1970; Nelson, 1982; Nuechterlein et al., 2008; Robertson et al., 1996; Christensen et al., 1994; Dureman and Sälde, 1959; Wechsler, 1958; Johansson and Zarit, 1991)).

Neuropsychological impairment is a core feature of schizophrenia (Reichenberg and Harvey, 2007; Zanelli et al., 2010); it emerges early and remains relatively stable throughout the course of the illness (Mesholam-Gately et al., 2009). The most severe impairment is reported in processing speed (Dickinson et al., 2007; Knowles et al., 2010), but deficits in episodic memory and working-memory have also been proposed as core features (Lee and Park, 2005). A similar profile of impairment has been reported in people with psychotic experiences (Kelleher et al., 2012a; Niarchou et al., 2013), but most of these studies have focused on child and adolescent samples, despite evidence that psychotic experiences are prevalent across the life course (Linscott and Van Os, 2013; van Os et al., 2009; Johns et al., 2004; McGrath et al., 2015). Only one study in our meta-analysis investigated the neuropsychological correlates of psychotic experiences across adulthood (Johns et al., 2004) and reported on a single cognitive domain. Moreover, previous studies have not adjusted for key sociodemographic confounders, whose importance is highlighted by the World Mental Health Surveys' finding of higher prevalences of psychotic experiences in middle- and high-income countries compared to low-income countries (McGrath et al., 2015). Finally, the association between psychotic experiences and neuropsychological functioning may be confounded by shared familial factors (D'Onofrio et al., 2013).

Table 2.1 Studies investigating neuropsychological functioning and psychotic experiences

Domain by Source	Number of participants	Age (years) at measurement of cognition	Age (years) at measurement of psychotic experiences	Rate of psychotic experiences (%)	Effect size (<i>d</i>)
IQ^a					
Polanczyk et al. 2010	2127	5	12	5.9	-.51
Kremen et al. 1998	547	4 & 7	23	3.2	-.61
Horwood et al. 2008	6384	8	12	13.8	-.08
Cannon et al. 2002	789	3-11	11	14.7	-.52
Pooled effect size					-.40
General cognition^b					
Niarchou et al. 2013	6784	8, 10 & 11	12	11.6	-.05
Kelleher et al. 2012	165	11-13	11-13	25.5	-.03
Barnett et al. 2012	2916	8, 11 & 15	53	22.3	-.16
Gur et al. 2014	4275	8-21	8-21	15.5	-.42
Johns et al. 2004	8520	16-74	16-74	5.5	-.34
Pooled effect size					-.19
Processing speed^c					
Niarchou et al. 2013	6784	8, 10 & 11	12	11.6	-.13
Kelleher et al. 2012	165	11-13	11-13	25.5	-.30
Gur et al. 2014	4275	8-21	8-21	15.5	-.29
Henderson et al. 1998	870	78	78	7.5	-.24
Ostling et al. 2004	245	85	85	14.3	-.56
Pooled effect size					-.20
Working memory^d					
Niarchou et al. 2013	6784	8, 10 & 11	12	11.6	-.07
Kelleher et al. 2012	165	11-13	11-13	25.5	-.09
Gur et al. 2014	4275	8-21	8-21	15.5	-.29
Ostling et al. 2004	245	85	85	14.3	-.33
Pooled effect size					-.18
Memory^e					
Kelleher et al. 2012	165	11-13	11-13	25.5	-.18
Gur et al. 2014	4275	8-21	8-21	15.5	-.32
Ostling et al. 2004	245	85	85	14.3	-.29
Pooled effect size					-.31

^aIQ measures include Vocabulary and Block Design subtests of Wechsler Preschool and Primary Scale of Intelligence-Revised (Wechsler, 1989) for Polanczyk et al.; Stanford-Binet Intelligence Scale (age 4 years)(Terman and Merrill, 1960) and Information, Vocabulary, Digit Span, Comprehension, Block Design, Picture Arrangement, and Coding subscales of Wechsler Intelligence Scale for Children (WISC) (age 7 years)(Wechsler, 1949) for Kremen et al.; WISC III (Wechsler, 1991) for Horwood et al.; and Peabody Picture Vocabulary Test (age 3 years)(Dunn and Dunn, 1997), Stanford-Binet Intelligence Scale (age 5 years)(Terman and Merrill, 1960), and WISC (ages 7, 9, and 11 years)(Wechsler, 1974) for Cannon et al.

^bGeneral cognition measures include Picture Completion, Picture Arrangement, Block Design, and Object Assembly subtests of WISC III(Wechsler, 1991) for Niarchou et al.; Wide Range Achievement Test 4 (Wilkinson and Robertson, 2006) for Kelleher et al.; Picture Intelligence, Reading, Sentence Completion, and Vocabulary (age 8 years), Arithmetic, Reading, Vocabulary, Verbal, and Nonverbal IQ (age 11 years), and Maths, Reading, Verbal, and Nonverbal IQ (age 15 years) from AH4 Group Test of Intelligence (Heim, 1970) for Barnett et al.; the Verbal Reasoning, Nonverbal Reasoning, and Spatial Processing subtests of the Computerized Neurocognitive Battery (CNB)(Gur et al., 2010) for Gur et al.; and National Adult Reading Test (Nelson, 1982) for Johns et al.

^cProcessing speed measures include Sky Search Task from Tests for Everyday Attention for Children (Robertson et al., 1996) and the Coding subtest of WISC III (Wechsler, 1991) for Niarchou et al.; Symbol Coding and Category Fluency in Trail Making Test from MATRICS neurocognitive battery (Nuechterlein et al., 2008) for Kelleher et al.; Symbol Letter Modalities Test (Christensen et al., 1994) for Henderson et al.; and Identical Forms Test (Dureman and Sälde, 1959) for Ostling et al.

^dWorking memory measures include Backward Digit Span and Arithmetic from WISC III (Wechsler, 1991) for Niarchou et al.; Spatial Span and Letter Number Span of Wechsler Memory Scale from MATRICS neurocognitive battery (Nuechterlein et al., 2008) for Kelleher et al.; Abstraction and Mental Flexibility and Attention and Working Memory subtests of CNB (Gur et al., 2010) for Gur et al.; and Digit Span for Ostling et al.

^eMemory measures include Hopkins Verbal Learning Test from MATRICS neurocognitive battery (Nuechterlein et al., 2008) for Kelleher et al.; Words, Faces, and Shapes subtests of CNB (Gur et al., 2010) for Gur et al.; and Thurstone Picture Memory Test(Dureman and Sälde, 1959) and Memory in Reality, Prose Recall, and Ten Word Memory Test (Johansson and Zarit, 1991) for Ostling et al.

In the present study we examined subclinical psychotic experiences and neuropsychological functioning in adults from an ethnically and sociodemographically diverse population. Our study was unique in examining the effects of 1) important confounders, including cannabis use and psychiatric morbidity, 2) age, and 3) confounding by familial factors on the association between psychotic experiences and neuropsychological functioning. We hypothesized that psychotic experiences would be associated with a profile of cognitive impairment similar, yet milder, to that of schizophrenia, characterized by specific deficits in processing-speed and memory seen in the context of a generalized deficit.

Methods

Sample

The South East London Community Health (SELCoH) study is a population-based household survey completed in 2010 in the two London boroughs of Lambeth and Southwark. The aim was to provide prevalence estimates of mental and physical health symptoms in an ethnically and socioeconomically diverse, geographically defined, inner-city community. A random sample of households was identified using the Small User Postcode Address File (<https://www.poweredbypaf.com/>), which has nearly complete coverage of private households in the United Kingdom. Introductory letters were sent to households, which were visited up to four times at different times of the day and week. When contact was made, written informed consent was sought from as many eligible (aged ≥ 16 years) members of the household as possible; all study participants provided written informed consent. Contact was established with 2070 private households, of which 1075 had at least one member interviewed, representing a 51.9% household participation rate. Of 2359 individuals eligible within the participating

households, 1698 (72.0%) participated (a detailed description can be found elsewhere (Hatch et al., 2011)). This study was approved by the research ethics committee of King's College London.

Procedure

Data were collected using a computer-assisted interview schedule, which was piloted to establish reliability, validity, and feasibility. Data were collected from June 1, 2008, to December 31, 2010. Participants received £15 for participation.

Measures

Psychotic experiences

The Psychosis Screening Questionnaire (PSQ) (Bebbington and Nayani, 1995) was used to measure psychotic experiences. The PSQ is an interviewer-administered questionnaire that assesses psychotic experiences in the preceding year and comprises five sections covering hypomania, thought disorder, paranoia, strange experiences and hallucinations. Items on hypomania were discarded because the focus was on psychosis. Each section has an initial probe, followed by secondary question(s), which establish the quality of psychotic experiences. The PSQ has been validated in two national surveys in the UK (Nazroo, 1997; Singleton et al., 2003). In this study, those who endorsed one or more secondary questions at the highest level on the PSQ were compared with those who did not (Johns et al., 2004) (**Appendix I, eTable 1**).

Neuropsychological functioning

Verbal knowledge was assessed using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), working memory with the Spatial Delayed Response Task (SDRT) (Glahn et al., 2003), visual memory with the Visual Object Learning Task

(VOLT)(Glahn et al., 1997) and processing speed with a digit symbol coding task (DSCT)(Tulsky et al., 1997; Glahn et al., 2007a) (**Appendix I, eTable 2**).

Neuropsychological tests were administered using a computer as in previous schizophrenia and bipolar disorder studies in which impairments of expected effect sizes were shown (Gold et al., 2010; Cannon et al., 2005; Calkins et al., 2005; Bachman et al., 2010; Glahn et al., 2007b). We calculated a general cognitive ability composite score as the first principal component of a factor analysis using all the neuropsychological tests administered (Burdick et al., 2006). Scores were transformed to an IQ-like score with mean of 100 and SD of 15. No cut-off for low IQ was applied since psychotic experiences are associated with cognitive deficits and exclusion of participants with low IQ may over-correct for differences in cognitive functioning.

Confounders

The interview established ethnicity, age and occupation classified according to the Registrar General (Rose, 1995) as professional (I), managerial/technical (II), skilled nonmanual (III-NM), skilled manual (III-M), semiskilled (IV), unskilled (V) and unclassified. Common mental disorders (CMD) were assessed using the Revised Clinical Interview Schedule (CIS-R)(Lewis et al., 1992), which asks about the following 14 symptom domains during the previous week: fatigue, sleep problems, irritability, worry, depression, depressive ideas, anxiety, obsessions, subjective memory and concentration, somatic symptoms, compulsions, phobias, physical health worries and panic. A score of 18 or more indicates presence of a common mental disorder. Good reliability and validity of the Revised Clinical Interview Schedule have been reported (Lewis et al., 1992; Jordanova et al., 2004). Cannabis use in the past year was also reported. Ethnicity, occupation, cannabis use and common mental disorders correlated significantly with both psychotic experiences and neuropsychological functioning, but

minimally with one another (**Appendix I, eTable 3**). Interactions of group (participants with psychotic experiences or control participants) by confounder (ethnicity, occupation, cannabis use and common mental disorders) with centred variables (Kraemer and Blasey, 2004) on all tests were not statistically significant except for the group by ethnicity interaction on IQ ($p=.03$).

Familial factors

We investigated familial factors by dividing cohabitants of participants with psychotic experiences into two groups. The first group included first-degree relative (e.g. biological child, biological sibling); the second non-genetically related cohabitants (e.g. spouse, non-biological child).

Data analysis

Data were analysed from May 6, 2014, to April 22, 2015. Analyses were completed in STATA software (version 13; Stata-Corp). Appropriate survey commands (svy) were used to generate robust SEs. All analyses of SELCoH data accounted for clustering by household inherent in the study design and were weighted for within-household nonresponse (Hatch et al., 2011).

We used linear regression (adjusting for ethnicity, occupational class, cannabis use in the last year and common mental disorders) to test the hypothesis that psychotic experiences would be associated with impairment in general cognitive ability (IQ). Because the profile of cognitive impairment in schizophrenia is characterized by specific deficits in processing speed and memory seen in the context of a generalized deficit and because different neural systems underlie performance on different neuropsychological tests, secondary analyses examined the association between psychotic experiences and individual neuropsychological test results. We applied a

Bonferroni correction to adjust for multiple comparisons in the secondary analyses, yielding a corrected significance level of $p < .007$ ($0.05/7$). We computed Cohen d effect sizes using postestimation margins (effect sizes of 0.2, 0.5 and 0.8 represent small, medium and large effects, respectively (Cohen, 1992)).

To explore the effect of age on the association between psychotic experiences and neuropsychological functioning local regression curves for age on the interaction of cognition by group were plotted for each test. To test the effect of age formally, we entered an interaction of group (psychotic experiences vs. comparison) by age (continuous) with centred variables (Kraemer and Blasey, 2004) into the regression model, adjusting for confounders as above. Linear regression analyses were subsequently stratified by age group (16-24, 25-34, 35-49 and ≥ 50 years), adjusting for confounders as above. Age categories were selected based on local regression curves and to ensure sufficient power. Owing to the exploratory nature of the age-stratified analyses, Cohen d effect sizes with associated 95% CIs only are presented herein.

Confounding by familial factors was first examined by plotting local regression curves for age on the interaction of cognition by group (controls, psychotic experiences, first-degree relatives and unrelated cohabitants) for each test and subsequently using linear regression, as described above, across the whole sample to ensure sufficient power. We conducted sensitivity analysis using a different cut-off for presence of psychotic experiences (i.e. yes to ≥ 1 secondary questions at any level (Morgan et al., 2009; Morgan et al., 2014)) using linear regression, as described above.

Results

Psychotic Experiences

Ten participants with missing PSQ data, 8 participants reporting a current or past diagnosis of psychosis and three participants currently taking antipsychotics were excluded from the analyses. The remaining 1677 participants were ethnically diverse (633 [37.7%] not white British), with a mean (SD) age of 40 (16.9) (range, 16-90 years). Seven hundred and thirty-three participants were male (43.7%).

Based on self-report and medication use, 11 participants (prevalence, 0.7%) had a psychotic illness, which is consistent with previous reports of prevalence (McGrath et al., 2008; Perälä et al., 2007). The one-year weighted prevalence of psychotic experiences, defined as positive responses to all secondary questions in one or more categories on the PSQ (Johns et al., 2004), included 171 participants (9.7%), which is consistent with findings from the World Health Survey (Nuevo et al., 2010). The group with psychotic experiences was more likely to be of a minority ethnic background, have a lower occupational status, have used cannabis in the past year and have a common mental disorder (**Appendix I, eTable 4**). Age differences in prevalence were not statistically significant.

Association of Psychotic Experiences with Neuropsychological deficits

Table 2.2 shows the relationship between psychotic experiences and neuropsychological performance before and after adjusting for confounders. The IQ impairment did not reach statistical significance when adjusting for confounders ($\beta=-3.78$, $t_{1261}=-1.91$, $p=.06$, Cohen $d=-0.22$). However, significant impairments were seen in the WTAR ($\beta=-4.21$, $t_{1347}=-3.02$, $p=.003$, Cohen $d=-0.37$), SDRT ($\beta=-1.15$,

$t_{1385}=-2.84, p=.005$, Cohen $d=-0.34$), VOLT ($\beta=-1.94, t_{1455}=-2.59, p=.01$, Cohen $d=-0.28$) and VOLT delay ($\beta=-0.66, t_{1411}=-2.37, p=.02$, Cohen $d=-0.24$). Impairments in the WTAR and SDRT scores remained statistically significant after correcting for multiple comparisons. No statistically significant impairment in the DSCT score was seen before or after adjusting for confounders.

Table 2.2 Group means and effect sizes before and after adjustments

Cognitive test	Mean (SD) score by group							
	Psychotic experiences		Comparison group		Effect size ^a	<i>p</i> ^b	Effect size ^c	<i>p</i> ^b
	N=1,506		N=171					
IQ	95.25	(16.58)	100.45	(14.77)	−.37	.001	−.22	.06
WTAR total	31.36	(15.78)	38.83	(12.64)	−.58	<.001	−.37	.003
SDRT total	20.97	(4.12)	22.51	(3.26)	−.46	<.001	−.34	.005
SDRT low load	11.32	(2.40)	12.02	(1.92)	−.36	.001	−.27	.02
SDRT high load	9.66	(2.13)	10.49	(1.85)	−.45	<.001	−.33	.004
VOLT	43.80	(8.45)	46.53	(7.06)	−.38	<.001	−.28	.01
VOLT delay	14.27	(2.97)	15.14	(2.75)	−.31	.001	−.24	.02
DSCT	40.63	(13.06)	42.17	(13.79)	−.12	.20	−.03	.73

Abbreviations: WTAR, Wechsler Test of Adult Reading; SDRT, Spatial Delayed-Response Task; VOLT, Visual Object Learning Task; DSCT, Digit Symbol Coding Task

^aUnadjusted

^bResults are statistically significant at the Bonferroni corrected level of $p<.007$

^cAdjusted for ethnicity and occupational class; cannabis use in last year and common mental disorders

We performed an exploratory analysis of the association between each psychotic experience (thought insertion, paranoia, strange experiences and hallucinations) and neuropsychological performance. All experiences were associated with cognitive impairment, but effect sizes varied (**Appendix I, eTable 5**). Frequency of individual symptoms did not allow stratification by age.

Association between Neuropsychological Functioning and Psychotic Experiences Stratified by Age

Previous studies have used samples consisting of mostly children and adolescents or of older adult samples, but inspection of **Table 2.1** suggests that the association between psychotic experiences and neuropsychological functioning may differ by age. **Figure 2.1** shows an overall age-associated cognitive decline in both groups, but also a difference in the severity of neuropsychological impairment associated with psychotic experiences at different ages. We found significant group-by-age interactions for all neuropsychological measures, including IQ ($p=.006$), WTAR ($p=.01$), SDRT ($p=.03$), VOLT ($p=.001$), VOLT delay ($p=.02$) and DSCT ($p=.01$) scores when adjusting for confounders. After stratifying by age group and adjusting for confounders, group differences in mean (SD) IQ (81.22 [15.97] vs 91.28 [14.31]; Cohen $d=-0.70$), WTAR (28.31 [13.83] vs 38.51 [11.50]; Cohen $d=-0.88$), SDRT (19.11 [4.77] vs 21.99 [3.42]; Cohen $d=-0.82$), VOLT (39.17 [8.23] vs 44.09 [6.51]; Cohen $d=-0.45$), and VOLT delay (13.09 [2.74] vs 14.34 [2.40]; Cohen $d=-0.52$) scores were medium to large in participants with psychotic experiences 50 years and older (**Figure 2.2**). Medium impairments in SDRT (21.27 [3.64] vs 22.62 [2.97]; Cohen $d=-0.45$) and VOLT (44.32 [5.84] vs 46.91 [5.74]; Cohen $d=-0.45$) scores were also found in participants aged 35 to 49 years with psychotic experiences and a medium impairment (30.81 [14.17] vs 37.60 [10.48]; Cohen $d=-0.62$) and a medium advantage (44.80 [6.61] vs 38.63 [8.43]; Cohen $d=0.74$) in WTAR scores in those aged 16 to 24 and 25 to 34 years, respectively. All other impairments in those younger than 50 years were small.

Figure 2.1 Local regression curves of neuropsychological functioning domains

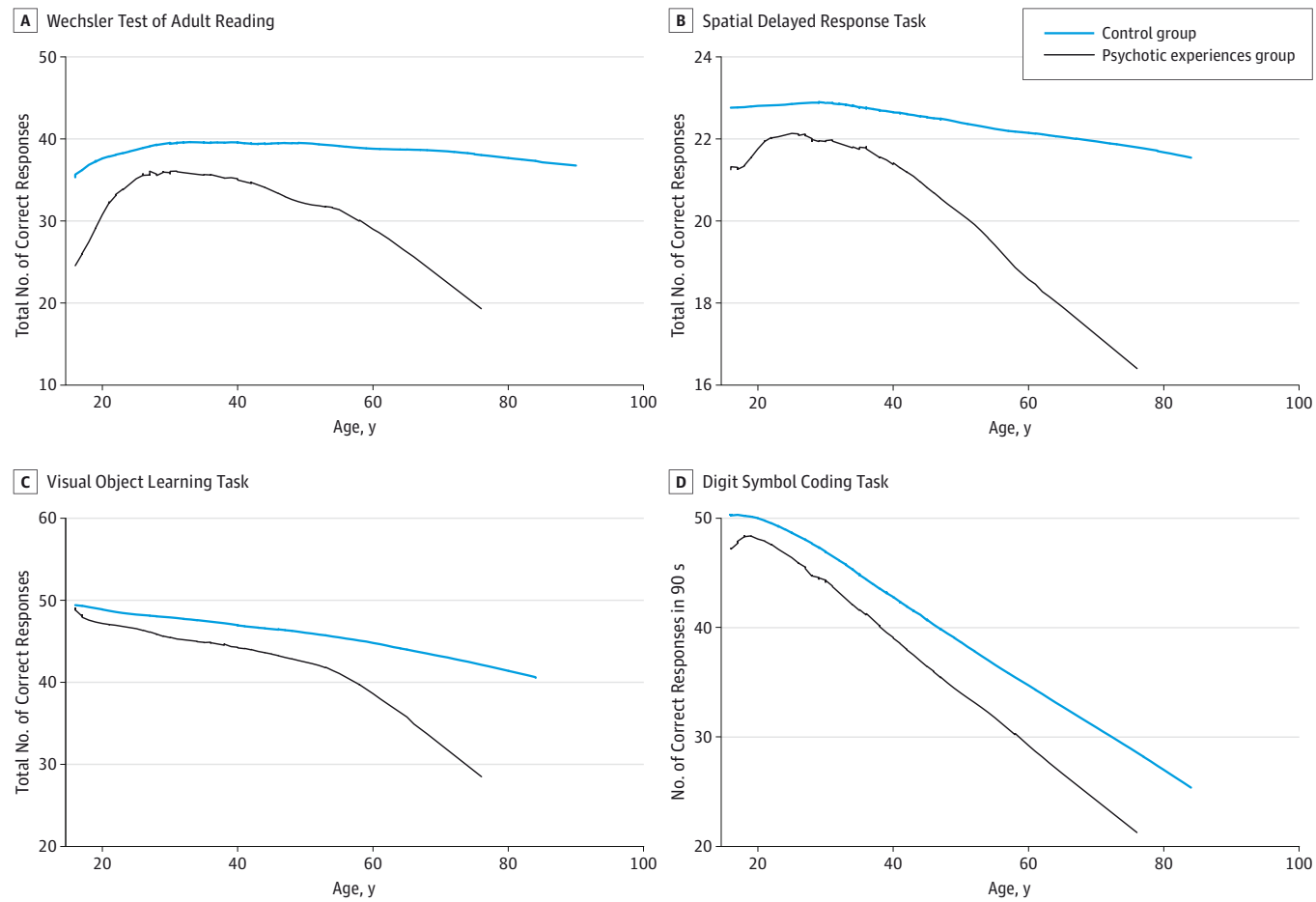
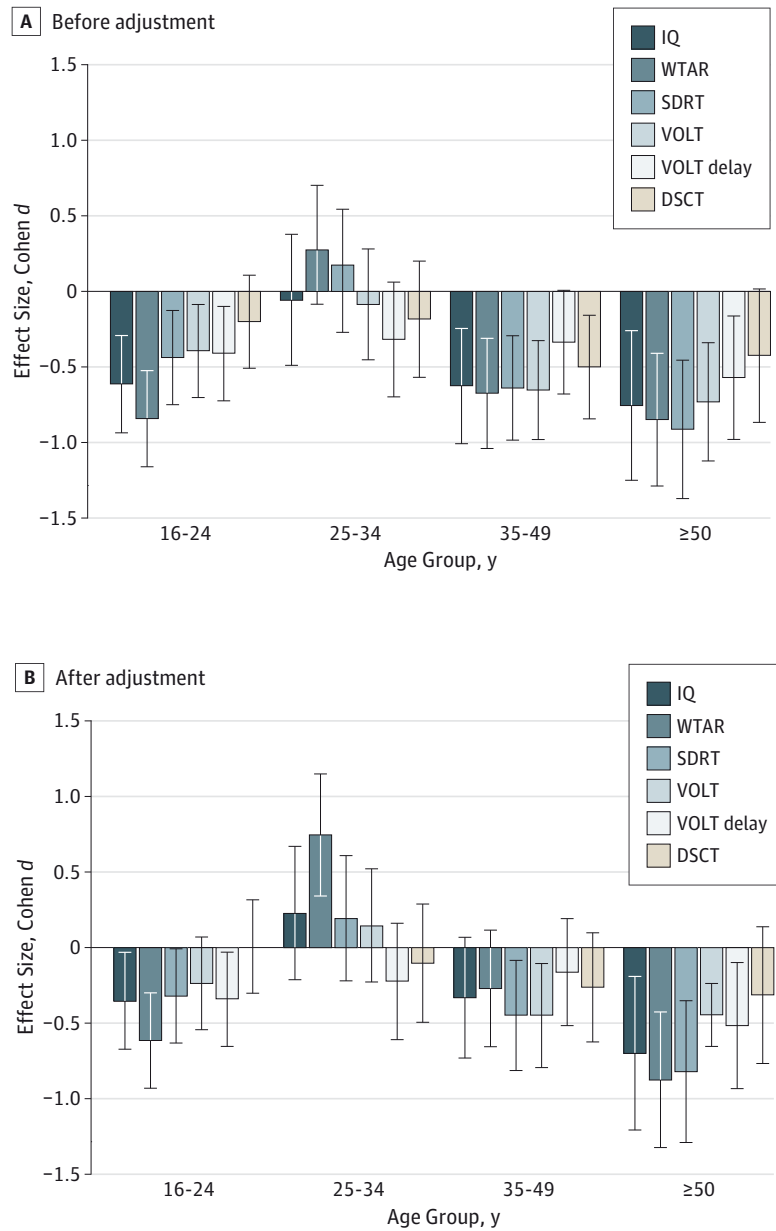


Figure 2.2 Effect sizes for each neuropsychological domain by age group before (top) and after (bottom) adjusting for confounders

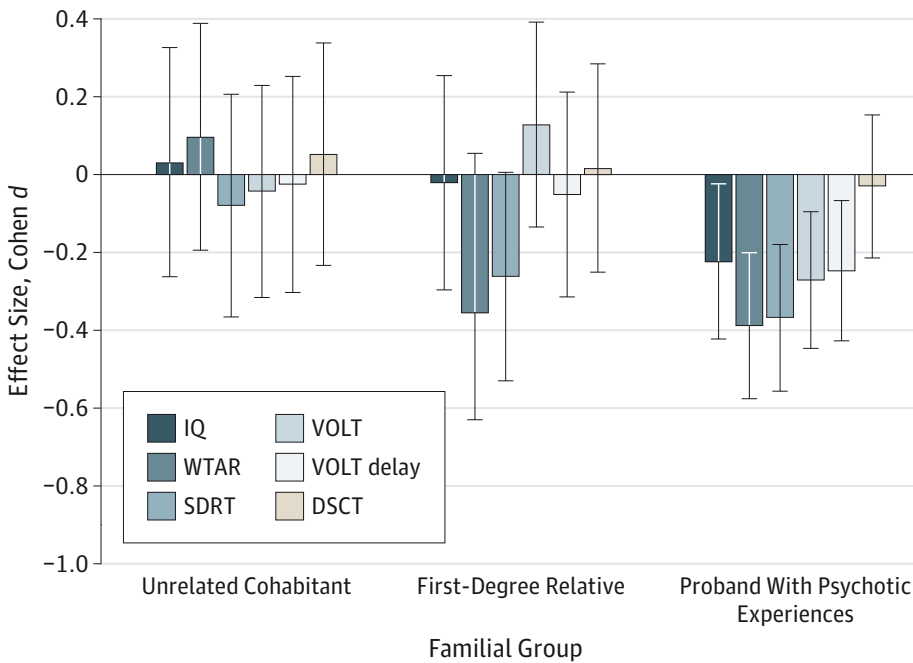


Sensitivity analysis using a different cut-off for the presence of psychotic experiences (Morgan et al., 2014; Morgan et al., 2009) produced similar results (**Appendix I, eFigure 2**). Adjusting additionally for educational level (**Appendix I, eTable 6 & eFigure 3**) also produced similar results.

Association between Neuropsychological Functioning and Psychotic Experiences by Familial Factors

Characteristics of each group are shown in **Appendix I, eTable 7**. Exploratory analyses (**Appendix I, eFigure 4**) suggested that WTAR performance was the most familial and VOLT performance was the least familial. First-degree relatives of probands were impaired on WTAR score ($\beta=-3.93$, $t_{1347}=-2.33$, $p=.02$, Cohen $d=-0.36$) after adjusting for confounders (**Figure 2.3**). Non-genetically related cohabitants did not show statistically significant neuropsychological deficits.

Figure 2.3 Effect sizes for each neuropsychological domain by familial group



Discussion

This study provides evidence that subclinical psychotic experiences are associated with mild neuropsychological impairment in adults. The magnitude of impairment in specific domains suggests impaired verbal and memory functions, but spared processing speed. Only older adults with psychotic experiences showed medium to large impairments in working memory and memory when adjusting for sociodemographic factors, psychiatric morbidity and cannabis use. First-degree relatives of probands also had a significant verbal, but not memory impairment. Our findings introduce new knowledge and propose new hypotheses regarding the neuropsychology of psychotic experiences in adults.

Our results are in line with those of the National Survey of Psychiatric Morbidity in Great Britain (Johns et al., 2004), which reported a small verbal IQ deficit in adults reporting psychotic experiences. Although not directly comparable to those from other previous studies, which have mostly focused on younger or older samples (Kelleher et al., 2012a; Henderson et al., 1998; Ostling et al., 2004; Niarchou et al., 2013), the adjusted effect sizes we report closely approximate the pooled effect sizes in our meta-analytic summary (**Table 2.1**). Adjustment for confounders attenuated the processing speed deficit, suggesting that the significant processing speed deficits reported in children and adolescents with psychotic experiences (Kelleher et al., 2012a; Niarchou et al., 2013) may be partly confounded. Alternatively, the cause of processing speed deficits associated with psychotic experiences may differ between adolescence and adulthood. Indeed, a recent study that used a dimensional categorization of psychotic experiences also did not find differences in processing speed between adults with low and high levels of psychotic experiences (Korponay et al., 2014).

Our findings highlight similarities, but also differences, between neuropsychological dysfunction associated with psychotic experiences versus disorders. Meta-analyses have shown the most severe cognitive impairment in schizophrenia to be in processing speed (Dickinson et al., 2007; Knowles et al., 2010). We found only a weak association between psychotic experiences and DSCIT performance. The discrepancy between a substantial processing speed impairment in psychotic disorder and a negligible impairment in psychotic experiences suggests that clinical psychosis is associated with increasing abnormality in processing speed (Reichenberg et al., 2010). Our findings add to a growing body of literature that challenges psychotic experiences as a subclinical phenotype of psychosis. Identification of factors associated with psychotic experiences that predict transition to psychotic disorder is needed if they are to be useful in the etiologic investigation of psychosis. Neuropsychological impairment, in processing speed specifically, may be one factor. Individuals with psychotic experiences and processing speed deficits may be most at risk for psychosis and this combination of risk factors warrants further longitudinal study.

This study was the first, to our knowledge, to investigate the effect of age on neuropsychological impairment associated with psychotic experiences in adults. Some studies suggest that these experiences are most prevalent in adolescence (Zammit et al., 2013) and old age (Tien, 1991), whereas meta-analyses have not found significant age differences (Linscott and Van Os, 2013; van Os et al., 2009; McGrath et al., 2015). In our sample, prevalence of psychotic experiences was greatest in the youngest group, but remained sizable in the other groups (**Appendix I, eTable 4**). Only older adults showed medium to large deficits in IQ, working memory and memory after adjusting for multiple demographic and psychosocial factors. Medium impairments in working memory and memory were seen in the group aged 35 to 49 years and in verbal

knowledge in the group aged 16 to 24. These findings highlight the heterogeneity of extended phenotypic expression associated with psychotic experiences throughout adulthood. Etiopathological pathways to subclinical psychotic experiences and neuropsychological dysfunction may be age dependent (**Appendix I, eFigure 5**). In young adults with psychotic experiences, neuropsychological impairment may signal a risk for general psychiatric disorders, possibly owing to psychosocial stress and/or substance use, however; in older adults, neuropsychological impairment may indicate vulnerability to accelerated cognitive aging. A faster trajectory of cognitive decline for patients with Alzheimer disease with concurrent delusions (Cummings and Victoroff, 1990) and hallucinations (Wilson et al., 2000) has been reported. Accelerated shrinkage of prefrontal and hippocampal regions seen in normal aging (Resnick et al., 2003; Raz et al., 2005) may lead to disrupted dopamine release and psychotic phenomena (Reeves et al., 2012), but also to more rapid cognitive decline.

By including cohabitants of participants with psychotic experiences, we explored potential mechanisms behind the association between psychotic experiences and cognition. First-degree relatives were significantly impaired on verbal knowledge, whereas unrelated cohabitants showed no impairment. Our findings suggest that a complex interplay of genetic, biological and psychosocial factors lies behind the association between psychotic experiences and neuropsychological impairment. This pattern of verbal knowledge impairment suggests common genetic and/or family environmental factors. On the other hand, unimpaired memory functions in both groups of cohabitants support biological and/or psychosocial effects of psychotic experiences on memory consistent with a causal effect.

Although we hypothesise that sociodemographic factors, cannabis use and common mental disorders are confounders, they could also be mediators or moderators.

Mediation and confounding are identical statistically, but can be distinguished conceptually (MacKinnon et al., 2000). Changes associated with the hypothalamic-pituitary-adrenal axis may be one area of investigation because the hypothalamic-pituitary-adrenal axis has been associated with all of these factors, and with psychosis and cognition (Arseneault et al., 2011). Shared genetic factors could be another area of investigation (Lee et al., 2013; Hatzimanolis et al., 2015). Examining interactions between multiple risk factors is important because complex multifactorial traits are likely to result from such interactions, and future studies with large samples are required for such investigations (Zammit et al., 2010).

The present study has a number of strengths. It is the first, to our knowledge, to use a large, heterogeneous, representative sample drawn from an urban community to investigate the effect of age and familial factors on the association between psychotic experiences and neuropsychological functioning while adjusting for important confounders. Nevertheless, several methodological limitations require consideration. First, the 51.9% household participation rate was high, but we were not able to characterize non-responders on demographic variables and rule out possible bias due to nonparticipation. However, the sample was representative of the local population on most sociodemographic characteristics (Hatch et al., 2011; Morgan et al., 2014). Second, psychotic experiences are fairly common in old age, presumably owing to neurodegenerative processes (Ballard et al., 1997) and we could not exclude participants with dementia. However, most of the participants in the oldest category were aged 50 to 65 years, when dementia is rare (Harvey et al., 2003) and medium to large impairments in IQ, WTAR, SDRT and VOLT scores (Cohen $d > 0.5$ for all) remained when we excluded participants older than 65 years. Third, interpretation of effect sizes generally depends on the assumption of normality, which held true for all tasks except

the WTAR, meaning that effect sizes in verbal knowledge may have been underestimated.

Moreover, those participants with poorer neuropsychological functioning may have been more likely to endorse psychotic experiences, and yet the association was not present at all ages or in all domains. We cannot infer from the current cross-sectional data that psychotic experiences lead to deficits in neuropsychological functioning. Another plausible explanation is that psychotic experiences and neuropsychological functioning are manifestations of common underlying processes (Toulopoulou et al., 2007; Fowler et al., 2012). Finally, the timing and history of psychotic experiences cannot be established from the PSQ, meaning that some psychotic experiences may be longstanding. The present data provide valuable insight into potential pathways to adult psychopathology, but future longitudinal studies that are able to disentangle their temporal sequence and to determine whether these findings also apply to lifetime psychotic experiences are needed.

Conclusions

The profile of cognitive impairment in adults with psychotic experiences differed from that found in psychotic disorders. Our findings highlight the importance of considering age, familial factors and the psychosocial context in neuropsychological studies of psychotic experiences.

Post-Article Comments

In the first study, young adults aged between 16 and 34 years old with psychotic experiences showed only small neuropsychological impairment and even above average scores in certain cognitive domains (**Figure 2.2**). The age range (16 to 34 years) of young adults in our sample coincides with the period during which most schizophrenia cases first manifest (Kessler et al., 2007). However, the cognitive profile of young adults reporting psychotic experiences differed substantially from that of patients with clinical psychotic disorder. Meta-analyses have shown the most severe cognitive impairment in schizophrenia to be in processing speed (Dickinson et al., 2007; Knowles et al., 2010), but we did not find a significant deficit in digit symbol coding performance in young adults with psychotic experiences. Young people who report psychotic experiences and show processing speed deficits may be most at risk for clinical psychotic disorder and these combined risk factors warrant further longitudinal study. The following study uses longitudinal data from the Avon Longitudinal Study of Parents and Children to chart cognitive developmental change between childhood and adulthood across general and specific functions, including processing speed. Young people with psychotic experiences without conversion to full psychosis, as well as individuals with clinical psychotic disorder, were compared to controls.

Cognitive Development from Infancy to Adulthood across the Psychosis Spectrum

Abstract

The course of cognitive impairment in young people with psychotic disorders and psychotic experiences is unclear. This study used longitudinal data from infancy through early adulthood to chart the emergence and course of deficits in general and specific cognitive functions. We examined whether a specific developmental course is observed in psychotic disorders versus psychotic experiences, as well as depression. Data from the Avon Longitudinal Study of Parents and Children (ALSPAC), which comprises all live births between 1991 and 1992 in Avon, UK, were analysed. All individuals who underwent cognitive testing at 18 months, 4, 8, 15 and 20 years, as well as psychiatric assessment at 18 years were included in the analyses. We compared participants with non-affective psychotic disorder, affective psychotic disorder, psychotic experiences and depression to controls on IQ measured through ages 18 months, 4, 8, 15 and 20 years, as well as measures of processing speed, working memory, language, visuospatial ability and attention at ages 8 and 20. The non-affective psychosis group showed continually increasing deficits in full-scale and performance IQ from age 18 months to 20 years (Cohen d of change $\Delta=-1.09$, $p=.019$; Cohen d of change $\Delta=-0.94$, $p=.008$). The depression group showed a small, increasing deficit in performance IQ (Cohen d $\Delta=-0.29$, $p=.04$). Between ages 8 and 20, the non-affective psychosis group exhibited increasing developmental lags (slower growth) in measures of processing speed, working memory and attention (Cohen d $\Delta=-0.68$, $p=.001$; Cohen d $\Delta=-0.59$, $p=.004$; Cohen d $\Delta=-0.44$, $p=.001$), as well as large, static deficits in measures of language and visuospatial ability (Cohen $d=-0.87$, $p=.005$; Cohen $d=-0.90$,

$p=.001$). Differences in the affective psychosis, psychotic experiences and depression groups did not reach Bonferroni corrected significance. Individuals who later developed non-affective psychosis already showed small to medium cognitive deficits across multiple cognitive domains in childhood. Deficits in fluid domains (e.g. processing speed and working memory) continued to worsen through adolescence and early adulthood, until they reached the magnitude seen in chronic schizophrenia patients. A progressive course of impairment across cognitive domains was not seen in depression, affective psychosis or, importantly, in those with subclinical psychotic experiences not transitioned to the full disorder.

Introduction

Cognitive impairment is a core feature of schizophrenia. Understanding its nature and course will help elucidate the pathophysiological processes that lead to the disorder.

There is clear evidence for cognitive deficits in children and adolescents who later develop schizophrenia, with an estimated average premorbid deficit of 8 IQ points (0.5 SD) (Woodberry et al., 2008). Larger deficits averaging around 14 IQ points (0.9 SD) are seen in adults with schizophrenia even at the first episode (Mesholam-Gately et al., 2009). Longitudinal studies investigating IQ change from before to after illness onset have shown evidence of increasing neuropsychological impairment (Meier et al., 2013). The extent and course of premorbid impairment, however, may differ between functions. While verbal deficits have shown a static course, emerging early and remaining stable, processing speed and working memory abilities have shown slower growth over time, resulting in increasing lags (Reichenberg et al., 2010).

Important questions remain regarding the course of neuropsychological impairment in schizophrenia. First, the timing of deficits is not well characterized. Therefore, it is

unclear whether deficits evolve during specific developmental periods. Previous studies have not been able to comprehensively chart cognitive functioning from childhood to adulthood. Adolescence is a critical risk period for schizophrenia (Weinberger, 1987; Murray and Lewis, 1987) and there is evidence for abnormal brain changes during this developmental period (Paus et al., 2008). Yet, only a few studies permit examination of cognitive development between late childhood and early adolescence (Reichenberg et al., 2010; Gochman et al., 2005) and studies spanning early childhood and adolescence are even scarcer, with mixed results (Agnew-Blais et al., 2015; MacCabe et al., 2013).

Second, do individuals with subclinical psychotic experiences have normal cognitive development? Cross-sectional studies of clinical high-risk samples have shown that individuals who transition to the clinical disorder manifest greater deficits in the domains of processing speed, memory and working memory than those who do not (Fusar-Poli et al., 2012; Addington and Barbato, 2012). Moreover, subclinical psychotic symptoms have been associated cross-sectionally with lags in verbal and complex cognitive abilities (Gur et al., 2014). However, longitudinal studies are few, with short follow-ups (Woodberry et al., 2013; Carrion et al., 2015).

Third, how specific are the cognitive deficits to schizophrenia? While cognitive deficits have been identified in various psychiatric disorders (Millan et al., 2012), the extent and course of deficits appears to differ between them (Meier et al., 2013; Zanelli et al., 2010). Major depression and bipolar disorder have generally been associated with milder deficits than schizophrenia (Millan et al., 2012) or, in the case of bipolar disorder, even above average intellect (MacCabe et al., 2010). It remains unclear, however, how these deficits develop and whether a course of increasing impairment is specific to schizophrenia.

Previous longitudinal neuropsychological studies have been unable to answer these key questions. The use of measures of scholastic achievement or IQ-proxies rather than standard measures has limited the conclusions that can be drawn from such studies. Moreover, the use of different neuropsychological tests across ages has made it difficult to establish true cognitive development change. Additionally, failure to assess neuropsychological functioning before adolescence, when prodromal symptoms are likely to first manifest, may lead to underestimates of the magnitude of cognitive decline that precedes illness onset. Finally, few studies have measured neuropsychological functioning longitudinally in other psychiatric disorders.

As part of an on-going population representative longitudinal study (the Avon Longitudinal Study of Parents and Children), we mapped IQ change from infancy (18 months), through childhood (age 8) and adolescence (age 15), to early adulthood (20 years). We focused on the period encompassing adolescence (from age 8 to 20) using identical measures of IQ and specific neuropsychological functions across ages. Subjects with non-affective psychotic disorder, affective psychotic disorder, subclinical psychotic experiences and depression were compared to control participants. We hypothesized that individuals with psychotic disorders would show increasing cognitive deficits, particularly in fluid abilities during the adolescent period. We hypothesized that individuals with psychotic experiences would show a similar, yet milder, profile of cognitive impairment.

Methods

Sample

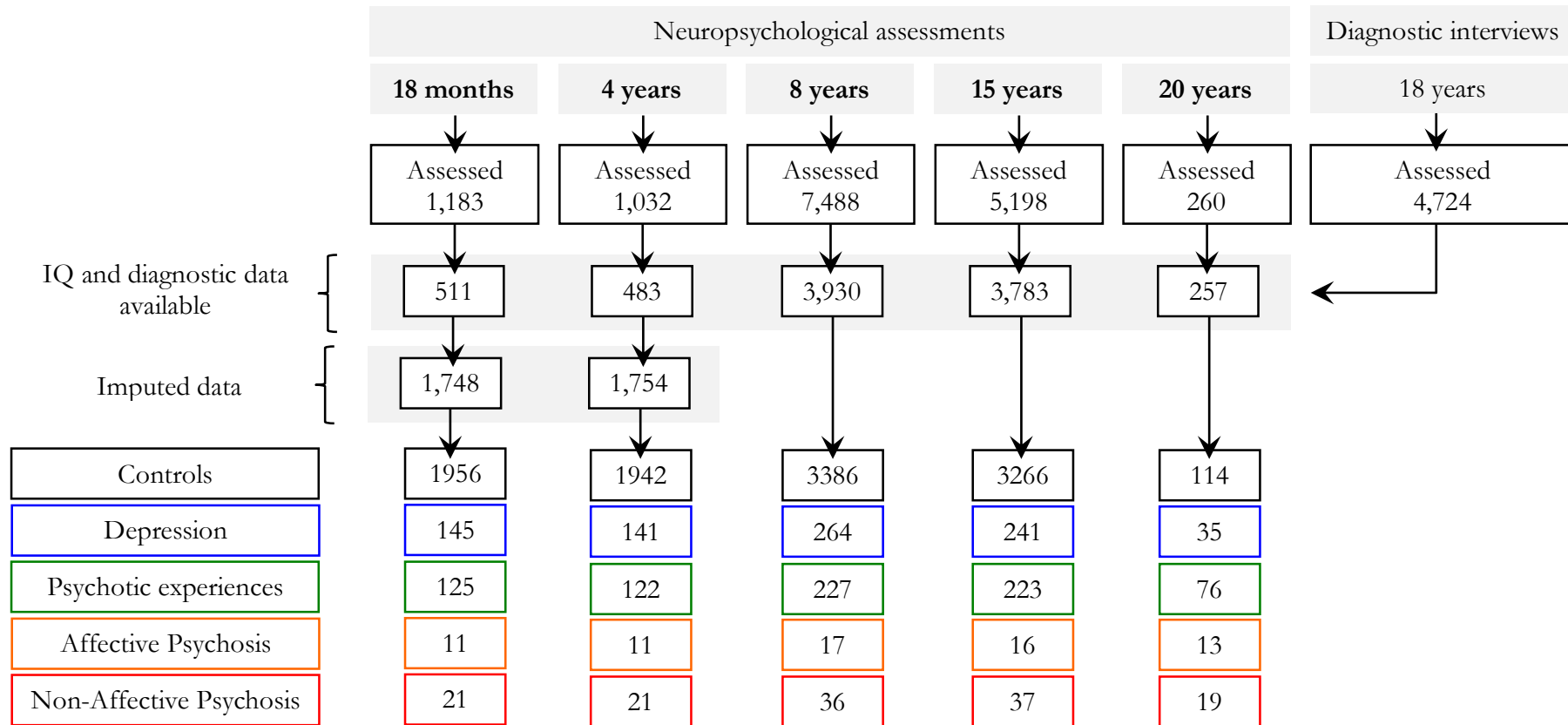
The sample comprised individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. ALSPAC recruited 14,541 pregnant women resident in

Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992, resulting in 14,062 live births (study website contains details of data available through a fully searchable data dictionary: <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>)(Fraser et al., 2013; Boyd et al., 2013). Regular data collection is on-going since September 6th 1990. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. All participants and/or their parents provided written informed consent.

IQ change from infancy, through childhood, adolescence and early adulthood

We used data from all available individuals who had undergone cognitive testing during at least one assessment wave (18 months, 4, 8, 15 and/or 20 years), and had also undergone diagnostic interviewing at age 18. Variable numbers of individuals were available for analyses at each time point (**Figure 3.1**).

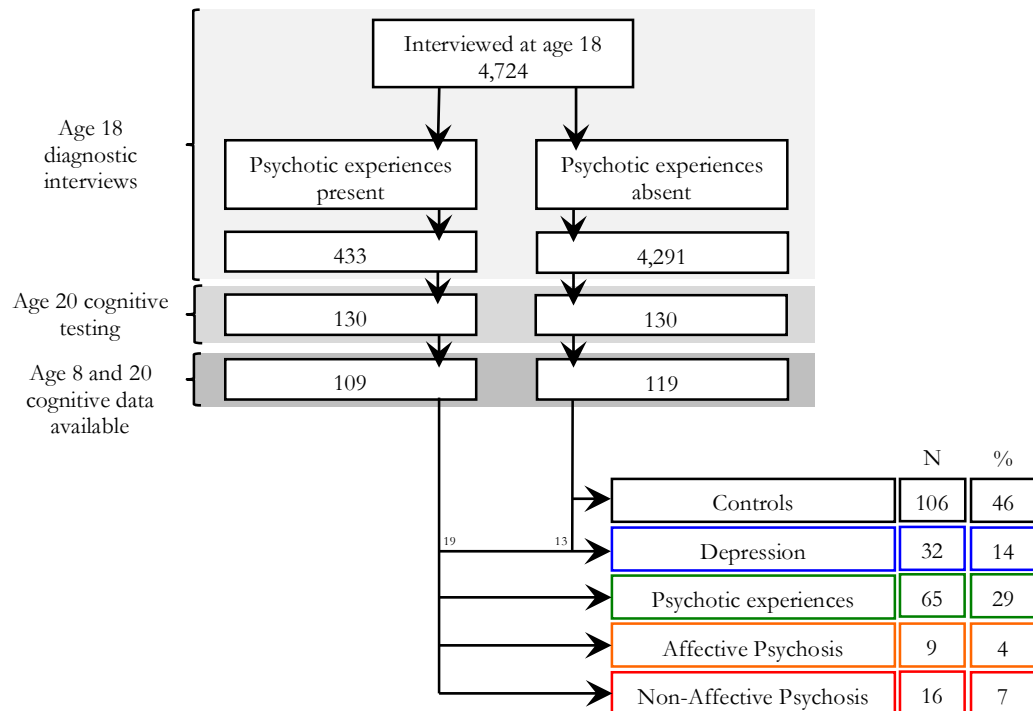
Figure 3.1 Data available at ages 18 months, 4, 8, 15 and 20 years



Cognitive developmental change between ages 8 and 20

A total of 4,724 young adults attended the age 18 assessment wave and underwent extensive psychological testing, including the Psychosis-Like Symptom interview (PLIKSi) (Zammit et al., 2013). Based on the PLIKSi, a case-control sample of 260 subjects (130 high-risk for psychosis (psychotic experiences present) and 130 controls (psychotic experiences absent)) underwent cognitive testing at age 20 (Drakesmith et al., 2016). All those who were rated as having psychotic experiences at age 18 and a random sample of participants who were rated as not having any psychotic experiences were invited for testing at age 20. Of this case-control sample of 260 subjects, 228 subjects who had also undergone cognitive testing at age 8 were available for analyses and are referred to as the high-risk longitudinal sample henceforth (**Figure 3.2**).

Figure 3.2 Flowchart depicting selection of high-risk longitudinal sample



Measures

Psychotic experiences

The semi-structured PLIKSi draws on the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). An introductory section on unusual experiences comprising six questions on derealization, depersonalization, self-unfamiliarity, dysmorphophobia, partial object perception and other nonspecific perceptual abnormalities is followed by 11 core questions eliciting key psychotic experiences: hallucinations (visual and auditory), delusions (e.g., persecution, reference, control and grandiosity, plus ‘unspecified’) and experiences of thought interference. Cross-questioning was used to establish the presence of symptoms and coding followed glossary definitions and rating rules for SCAN. Interviewers were specially trained psychology graduates. Interviewers rated psychotic experiences as not present, suspected or definite. Unclear responses after probing were always ‘rated down’ and symptoms were rated as definite only when a clear example was provided. A psychiatrist rated samples of recorded interviews at regular intervals to ensure correct ratings by interviews.

Psychotic disorder

If interviewers rated experiences as suspected or definitely psychotic, they also asked about frequency; impact on affect, social function, and educational/occupational function; help seeking; age at onset; and attributions. Individuals were classified as having a psychotic disorder if they reported definite psychotic experiences not attributable to the effects of sleep or fever that had occurred at least once per month over the previous 6 months and either caused severe distress, had a markedly negative impact on social or occupational function, or led to help seeking. Individuals also met diagnostic criteria for psychotic disorders as defined by the DSM-IV and ICD-10, since they experienced regular psychotic phenomena that caused them severe distress or

substantially impaired their functioning.

For inter-rater reliability the interviewers recorded audio interviews at three time points, approximately 6 months apart, across the clinic duration (75 interviews in total). The average kappa value of psychotic experiences was 0.83, with no evidence of differences across time. Test-retest reliability was assessed using 162 individuals reinterviewed after approximately 47 days ($\kappa=0.76$, $SE=0.078$), 46 of whom were reinterviewed by the same interviewer ($\kappa=0.86$, $SE=0.136$).

Depression

Depression was measured at age 18 using the computerized version of the Clinical Interview Schedule–Revised (CIS-R)(Lewis et al., 1992), which derives a diagnosis of depression according to ICD-10 criteria. The CIS-R has been widely used within community samples and is fully standardized and reliable as a self-administered computerized measure (Lewis et al., 1992; Patton et al., 1999; Bell et al., 2005; Brugha et al., 2005; Bebbington et al., 2003).

Neuropsychological functioning

Trained psychologists administered all neuropsychological tests. IQ was assessed at 18 months using the Griffiths Mental Development Scales-Revised (GMDS-R)(Griffiths and Huntley, 1996), age 4 using the Wechsler Preschool and Primary Scale of Intelligence Revised (WPPSI-R)(Wechsler, 1989), age 8 using the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III)(Wechsler, 1991), age 15 using the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999) and age 20 using the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III)(Wechsler, 1991)(see **Table 3.1** for list of available tests and **Table 3.2** for description of tests). Full-scale, verbal and performance IQ scores were calculated. Performance IQ was not available

at 18 months. In order to examine developmental growth in specific cognitive functions, identical versions of the digit symbol coding, digit span, vocabulary and block design subtests of the WISC-III, and the sky search task from the Tests of Everyday Attention for Children (Robertson et al., 1996), were administered at ages 8 and 20. WISC-III subtests were piloted on a sample of adults prior to the study in order to rule out ceiling effects. No cut-off for low IQ was applied since psychotic disorders are associated with cognitive deficits and exclusion of participants with low IQ may over-correct for differences in cognitive functioning.

Confounders

We examined age, gender, maternal education and medication as confounders. While all participants underwent testing during the same year at each assessment wave, they were not tested at exactly the same age. Four participants reported being prescribed medication for psychotic experiences during the PLIKSi at age 18 years.

Table 3.1 Cognitive tests available at ages 18 months, 4, 8, 15 and 20 years

Assessment Age	18 months	4 years	8 years	15 years	20 years
Cognitive Battery	Griffiths Mental Development Scales Revised	Wechsler Preschool and Primary Scale of Intelligence Revised	Wechsler Intelligence Scale for Children 3rd edition*	Wechsler Abbreviated Scale of Intelligence**	Wechsler Intelligence Scale for Children 3rd edition**
Full-Scale IQ subtests	Locomotor Social Language Coordination Performance	Object assembly Block design Mazes Picture completion Geometric design Information Comprehension Arithmetic Vocabulary Similarities	Object assembly Block design Picture completion Coding Picture arrangement Information Comprehension Arithmetic Vocabulary Similarities Digit span	Matrix Vocabulary	Block design Coding Vocabulary Digit span
Verbal IQ subtests	Language	Information Comprehension Arithmetic Vocabulary Similarities	Information Comprehension Arithmetic Vocabulary Similarities Digit span	Vocabulary	Vocabulary Digit span
Performance IQ subtests	-	Object assembly Block design Mazes Picture completion Geometric design	Object assembly Block design Picture completion Coding Picture arrangement	Matrix	Block design Coding

*Alternate item short form

**Alternate subtest short form

Table 3.2 Description of individual cognitive subtests

Battery	Subtest	Description
Griffiths Mental Development Scales	Locomotor	Assesses gross motor skills including balance, and coordination and control of movements. Items include age-appropriate activities such as walking up and down stairs, running and jumping.
	Social	Assesses developing abilities that contribute to independence and social development. Items include using a spoon competently to feed self, asking for things at table, helping to dress or undress self.
	Language	Assesses receptive language, expressive language and hearing (in the sense of active listening). Items include listening to stories, identifying objects and use of word combinations.
	Coordination	Assesses fine motor skills, manual dexterity and visual monitoring skills. Items include pouring water from one container to another, building a tower of bricks and throwing a ball into a basket.
	Performance	Assesses the way in which coordination skills are applied in novel situations. Items include unwrapping to find a toy or cube, putting a lid back on a box and opening a screw toy.
Wechsler Preschool and Primary Scale of Intelligence	Object assembly	Assesses visual perception and construction ability. Cut-up cardboard figures of familiar objects (puzzles) are given in order of increasing difficulty. The subject must construct the whole visual object from its parts within time constraints.
	Block design	Assesses visual-spatial organization, executive planning, and problem solving skills. The subject is required to put together red and white blocks in a pattern according to specific designs being displayed.
	Mazes	Assesses attention to detail, planning, perceptual organization and fine motor control. The subject is required to solve pencil and paper mazes of increasing difficulty.
	Picture completion	Assesses visual discrimination and reasoning. It requires knowledge of a variety of common objects and scenes. Subjects are shown incomplete pictures of human features, familiar objects or scenes arranged in order of difficulty and are asked to identify the missing part.
	Geometric design	Assesses visual perception, visual-motor organization, fine motor coordination and attention to detail. Includes two types of tasks where the subject is required to 1) match a pictured design from an array of four designs and 2) draw a copy of a geometric figure from a printed model.
	Information	Assesses general knowledge, the ability to acquire and store knowledge in long-term memory, to access it, and to express it verbally. Items include questions of increasing difficulty about history, geography and art.
	Comprehension	Assesses verbal ability, logical reasoning and understanding of relationships. Items include questions of increasing difficulty about general principles and social situations.
	Arithmetic	Assesses numerical knowledge, short-term memory, attention, and concentration. Subjects are presented with arithmetic problems of increasing difficulty in story format.
	Vocabulary	Assesses language skills such as the ability to acquire word meanings, recall them and express them. Items include questions about the meaning of words (e.g., What does winter mean?).
	Similarities	Assesses verbal concept formation, reasoning and the ability to categorize and conceptualize information available in semantic memory. Subjects are required to explain what a pair of words has in common, with word-pairs ranging in difficulty from concrete relations to abstract ones.
Wechsler Intelligence Scale for Children	Object assembly	See above
	Block design	
	Picture completion	
	Information	
	Comprehension	
	Arithmetic	Assesses psychomotor speed, coordination and attention. Better performance also depends on incidental learning. A key that pairs symbols and numbers is presented. Within a time constraint, the child is requested to fill in rows containing blank squares (each with a randomly assigned number above it) using the key.
	Vocabulary	
	Similarities	
	Coding	
	Picture arrangement	
	Digit span	Assesses short-term auditory memory and attention. Requires the subject to repeat a sequence of numbers (with increasing numbers of digits) in order (the forward component) and a different series of digits in reverse order (the backward component).
Wechsler Abbreviated Scale of Intelligence	Matrix	Assesses visual information processing and abstract reasoning skills. The subject views an incomplete matrix or series and selects the response option that completes the matrix or series.
	Vocabulary	See above

Data analysis

Our analyses compared five, mutually exclusive groups based on clinical interviews at age 18: 1) non-affective psychosis (psychotic disorder), 2) affective psychosis (comorbid for psychotic disorder and depression), 3) psychotic experiences, 4) depression and 5) healthy controls. Participants comorbid for psychotic experiences and depression were assigned to the depression group.

IQ change from infancy, through childhood, adolescence and early adulthood

Standardized full-scale and verbal IQ from all available individuals at ages 18 months, 4, 8, 15 and 20 years, as well as performance IQ at ages 4, 8, 15 and 20 years, were used to chart neuropsychological functioning through development. Multilevel random regression analysis was applied in STATA software (version 14; Stata-Corp), using the *xtmixed* command to fit linear mixed models. All models included fixed-effects for group (control, depression, psychotic experiences, affective psychosis and non-affective psychosis) and age (18 months, 4, 8, 15, 20 years), group-by-age interactions and random effects for age. Cohen *d* (Cohen, 1992) effect sizes were computed using marginal means obtained during postestimation procedures. Following Cohen, *d* effect sizes of 0.2, 0.5 and 0.8 were interpreted as reflecting small, medium and large effects respectively (Cohen, 1992). Data were imputed for full-scale and verbal IQ at ages 18 months and 4 years, and for and performance IQ at age 4. Twenty-eight measures were included in the imputation model and 50 datasets were imputed (**Appendix II, Methods**).

Sensitivity analyses were conducted to determine whether the different sampling frame at age 20 could lead to bias in results. First, we used individual sampling weights at age

of inclusion to determine whether the different sampling frame at age 20 could lead to bias in results. Second, we included only participants with data available at age 20.

Cognitive developmental change between ages 8 and 20

Full-scale, verbal and performance IQ scores were used to examine change in general cognition between childhood (age 8) and adulthood (age 20) in the high-risk longitudinal sample. Raw scores on the digit symbol coding, digit span, vocabulary, block design and sky search subtests were used to examine specific cognitive developmental change. Raw scores, rather than age-corrected scaled scores, were used. Scaled scores are the same at all ages in order to facilitate interindividual comparisons, therefore obscuring growth over time (Reichenberg et al., 2010). The use of raw scores, on the other hand, enables measurement of cognitive developmental growth. Multilevel random regression analysis was applied as above. Models were adjusted for potential confounders (above) and subsequently for all other neuropsychological tests. Since multiple neuropsychological tests were used, a Bonferroni corrected significance level of $.05/6 = p < .008$ was adopted to allow for repeated testing, although this is likely to be conservative. Cohen d effect sizes were computed as above.

Results

IQ change from infancy, through childhood, adolescence and early adulthood

Demographic characteristics of the sample are shown in **Table 3.3**. **Figure 3.3** shows standardized full-scale, verbal and performance IQ scores and Cohen d effect sizes at 18 months, 4, 8, 15 and 20 years, with model statistics shown in **Table 3.4**. The non-affective psychosis group showed monotonically increasing full-scale, verbal and performance IQ deficits from 18 months to 20 years, with overall declines equal to

Cohen $d=-1.09$, $p=.02$; Cohen $d=-0.69$, $p=.07$; Cohen $d=-0.94$, $p=.008$ respectively (Table 3.4).

The depression group showed an increasing performance IQ deficit from 18 months to 20 years, with an overall decline equal to Cohen $d=-0.29$, $p=.04$. There was insubstantial evidence for cognitive deficits in the psychotic experiences and affective psychosis groups, with no statistically significant results (Table 3.4).

The sensitivity analyses allowing for the different sampling fractions at 20 (Figure 3.4) and using only individuals with data available at age 20 (Figure 3.5) showed similar patterns of results. To supplement the analyses utilizing all available data, we also examined IQ change exclusively in those with data available at all time points, again finding a similar pattern of results (Figure 3.6).

Table 3.3 Demographic characteristics of the sample at each assessment wave

	18 months n=511	4 years n=483	8 years n=3930	15 years n=3783	20 years n=257
Age in years, mean (SD)	1.53 (0.03)	4.07 (0.03)	8.65 (0.29)	15.45 (0.27)	20.06 (0.55)
Male, N (%)	238 (47.6)	229 (47.1)	1679 (44.1)	1686 (44.6)	90 (35.0)
Maternal education, N (%)					
Low	74 (15.0)	70 (14.6)	592 (16.5)	588 (16.7)	46 (19.2)
Middle	176 (35.7)	172 (35.8)	1189 (33.1)	1187 (33.8)	87 (36.3)
High	243 (49.3)	238 (49.6)	1809 (50.4)	1742 (49.5)	107 (44.6)

Figure 3.3 Standardized scores and effect sizes by group at ages 18 months, 4, 8, 15 and 20 years

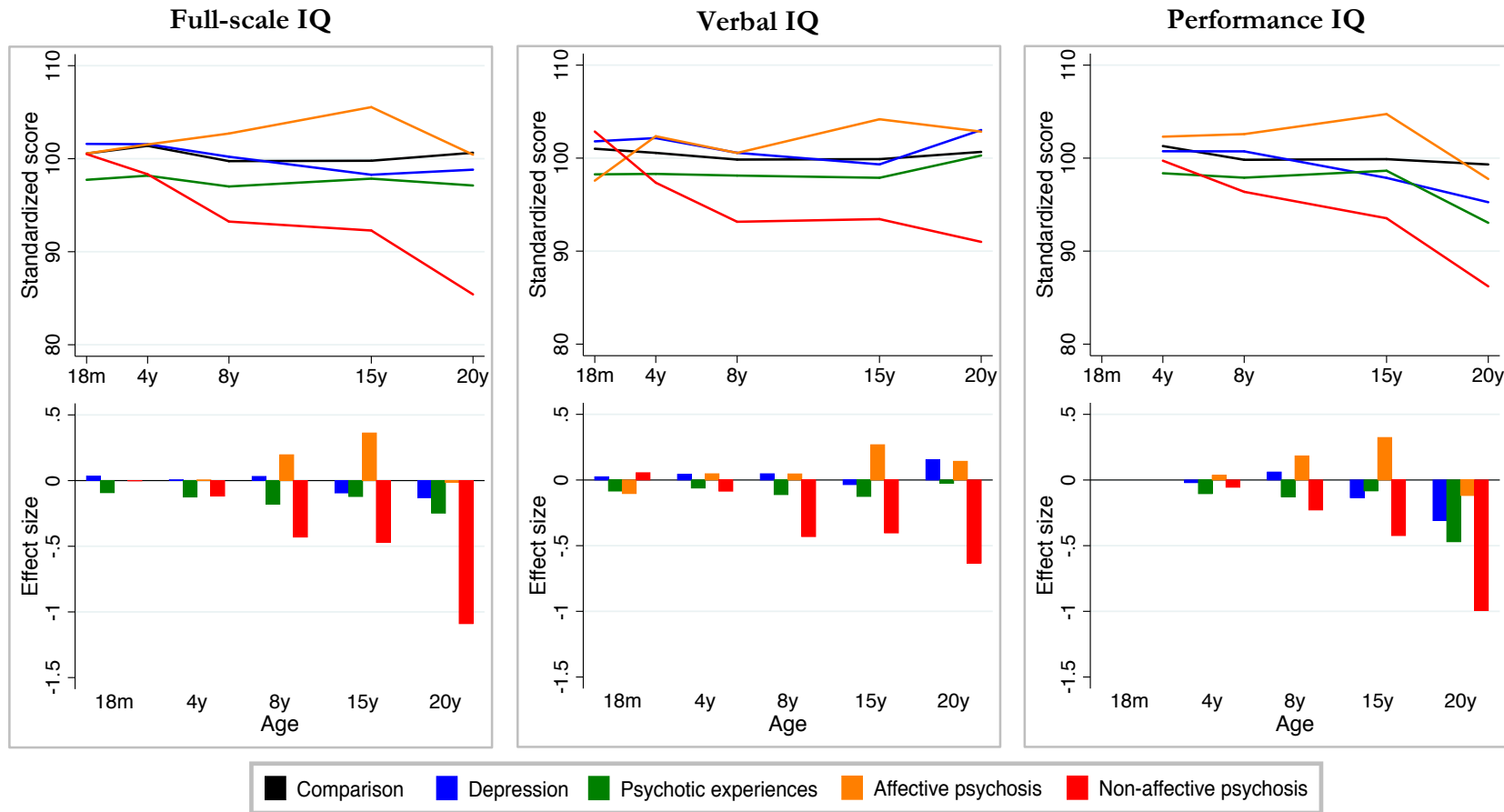


Table 3.4 Group and group-by-age interaction effects of multilevel random regression analysis on full-scale, verbal and performance IQ at ages 18 months, 4, 8 15 and 20 years*

Non-affective psychosis (n=19-37)						Affective psychosis (n=11-17)				
Group effect	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size
Full-scale IQ	94.9	-0.06	4.78	.9	-0.23	103.0	0.01	5.95	.9	0.12
Verbal IQ	95.7	1.85	4.14	.7	-0.18	101.5	-3.43	6.28	.6	0.05
Performance IQ	95.7	-1.57	4.23	.7	-0.22	103.2	1.01	5.68	.9	0.15
Group-by-age	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ
Full-scale IQ	-15.1	-0.58	0.25	.02	-1.09	-0.1	0.16	0.28	.6	-0.01
Verbal IQ	-11.9	-0.42	0.23	.07	-0.69	5.3	0.33	0.31	.3	0.25
Performance IQ	-13.5	-0.64	0.24	.008	-0.94	-4.5	-0.09	0.31	.8	-0.15
Psychotic experiences (n=76-223)						Depression (n=35-264)				
Group effect	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size
Full-scale IQ	98.0	-2.82	2.01	.2	-0.11	100.0	1.04	1.76	.6	-0.01
Verbal IQ	98.2	-2.75	1.91	.2	-0.08	100.8	0.79	1.62	.6	0.02
Performance IQ	98.2	-2.93	1.92	.1	-0.10	99.5	-0.56	1.67	.7	-0.03
Group-by-age	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ
Full-scale IQ	-0.6	0.06	0.11	.5	-0.16	-2.8	-0.16	0.11	.1	-0.17
Verbal IQ	2.0	0.10	0.11	.3	0.06	1.2	-0.07	0.10	.5	0.13
Performance IQ	-5.3	-0.07	0.12	.5	-0.37	-5.5	-0.24	0.12	.04	-0.29

*Results in bold signify $p < .05$

Figure 3.4 Standardized scores and effect sizes by group at ages 18 months, 4, 8, 15 and 20 years for sensitivity analysis with sampling weights

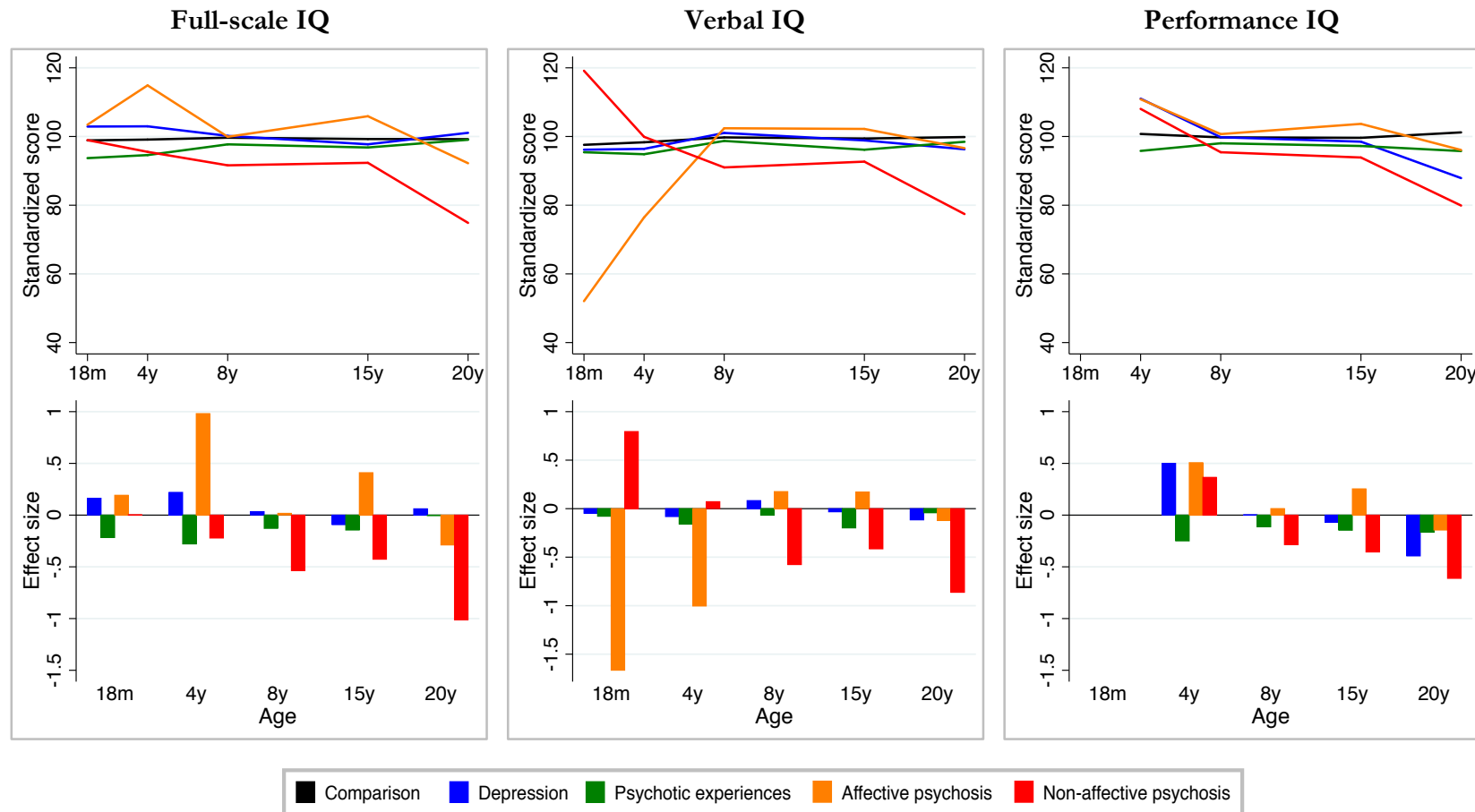


Figure 3.5 Standardized scores and effect sizes by group at ages 18 months, 4, 8, 15 and 20 years for sensitivity analysis including only individuals with available age 20 data

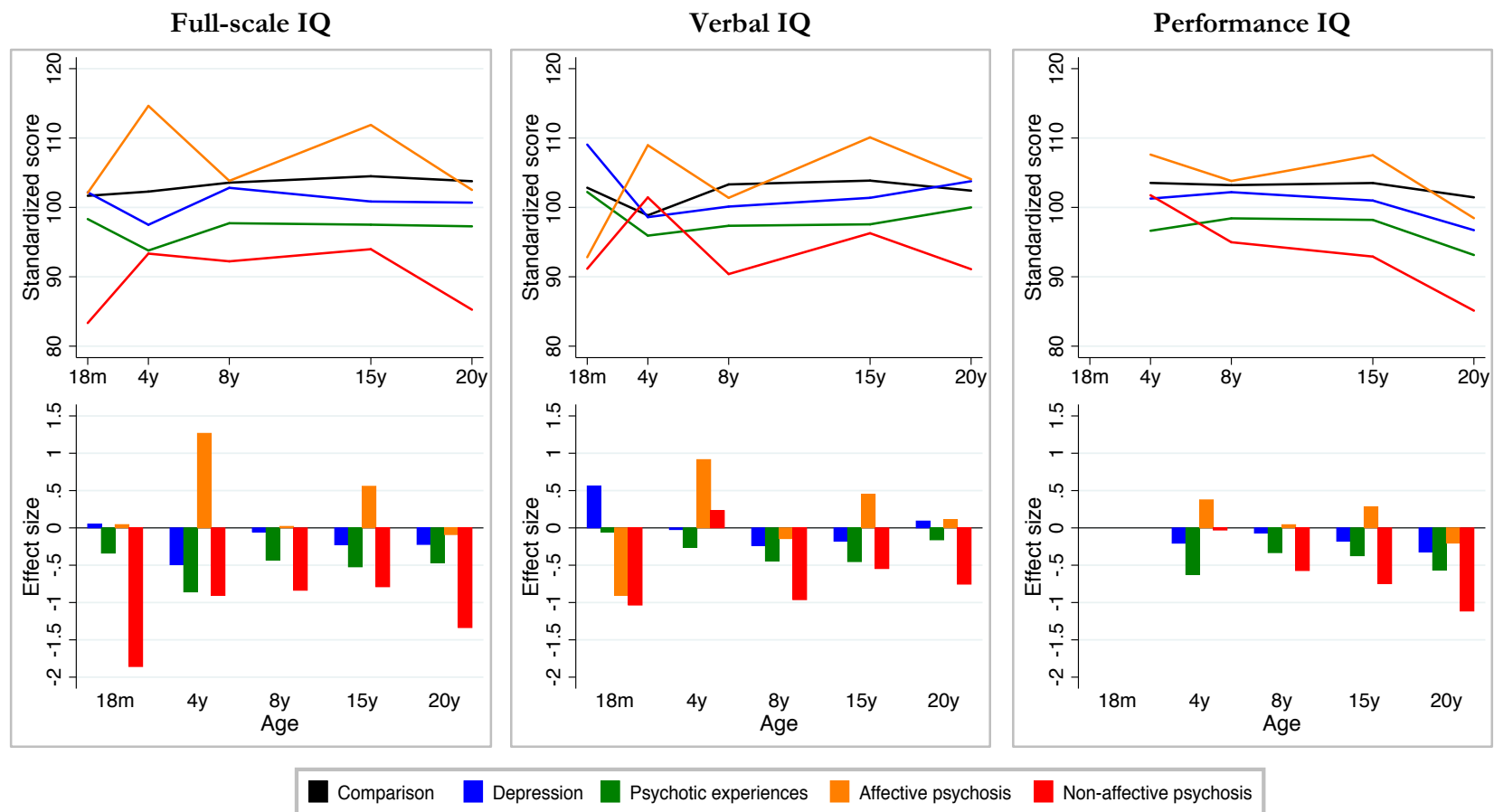
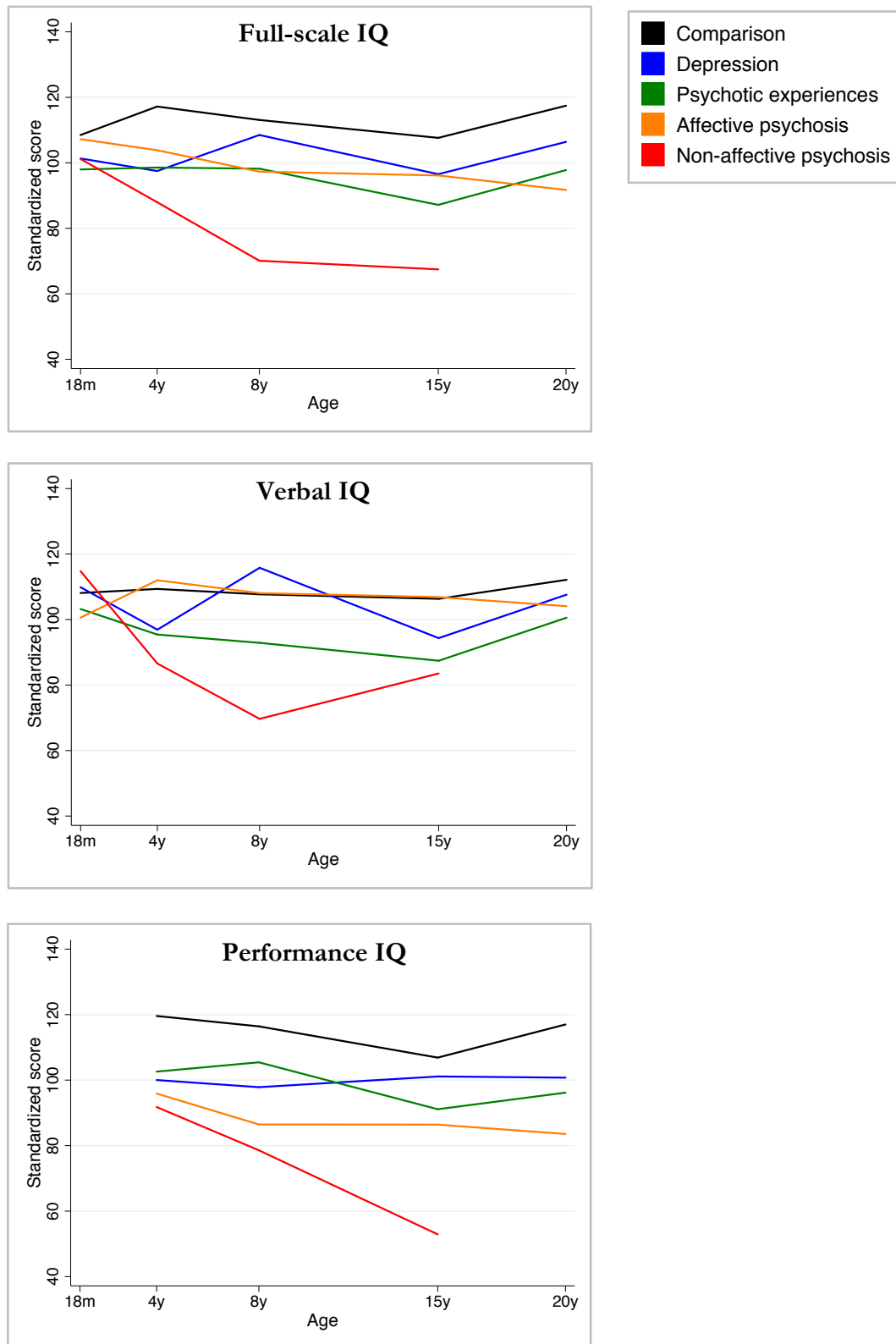


Figure 3.6 Standardized scores by group at ages 18 months, 4, 8, 15 and 20 years for individuals with data available at all ages



Cognitive developmental change between ages 8 and 20

Full-scale, verbal and performance IQ

Demographic characteristics of the high-risk longitudinal sample are shown in **Table 3.5**. **Figure 3.7** shows unadjusted scores and Cohen d effect sizes at ages 8 and 20 years, with model statistics shown in **Table 3.6**. The non-affective psychosis group showed significant main effects on full-scale IQ (Cohen $d=-1.17$, $p=.004$) and verbal IQ (Cohen $d=-0.99$, $p=.007$), as well as a significant group-by-age interactions on full-scale (Cohen d of change $\Delta=-0.54$, $p=.005$) and performance IQ (Cohen d $\Delta=-0.61$, $p=.002$), suggesting increasing full-scale and performance IQ deficits and a static verbal IQ deficit between ages 8 and 20. The psychotic experiences group showed main effects on full-scale (Cohen $d=-0.45$, $p=.01$) and verbal IQ (Cohen $d=-0.31$, $p=.01$), as well as a group-by-age interaction on performance IQ (Cohen d $\Delta=-0.22$, $p=.04$), which did not reach Bonferroni corrected significance. There was insubstantial evidence for cognitive deficits in the depression and affective psychosis groups, which showed no statistically significant results.

Table 3.5 Demographic characteristics of the high-risk longitudinal sample (n=228)

Male, N (%)	80 (35.1)
Maternal education, N (%)	
Low	39 (18.1)
Middle	79 (36.6)
High	98 (45.4)

Specific cognitive functions

The non-affective psychosis group showed statistically significant main effects, but not group-by-age interactions, on vocabulary (Cohen $d=-0.87$, $p=.005$) and block design (Cohen $d=-0.90$, $p=.001$), suggesting static language and visuospatial deficits between ages 8 and 20. The psychotic experiences group also showed main effects on

vocabulary (Cohen $d=-0.33$, $p=.02$) and block design (Cohen $d=-0.44$, $p=.01$), which did not reach Bonferroni corrected significance. Statistically significant group-by-age interactions for the non-affective psychosis group on digit symbol coding (Cohen $d \Delta=-0.68$, $p=.001$), digit span (Cohen $d \Delta=-0.59$, $p=.004$) and sky search (Cohen $d \Delta=-0.44$, $p=.001$) tests suggested increasing lags in processing speed, working memory and attention between ages 8 and 20. The psychotic experiences group showed significant group-by-age interactions on the digit symbol coding and sky search (Cohen $d \Delta=-0.29$, $p=.02$ and Cohen $d \Delta=-0.16$, $p=.04$ respectively), which did not reach Bonferroni corrected significance. The affective psychosis group showed a trend towards a group-by-age interaction on the digit symbol coding (Cohen $d \Delta=-0.45$, $p=.08$). There was insubstantial evidence for cognitive deficits in the depression group, which showed no statistically significant results.

Adjusting for confounders

After adjusting for age, gender, maternal education and medication (**Table 3.6**) the main effects for the non-affective psychosis group on full-scale (Cohen $d=-0.96$, $p=.04$) and verbal IQ (Cohen $d=-0.80$, $p=.03$), vocabulary (Cohen $d=-0.59$, $p=.09$) and block design (Cohen $d=-0.53$, $p=.04$), as well as the group-by-age interaction on full-scale IQ (Cohen $d \Delta=-0.54$, $p=.01$), were no longer statistically significant at the Bonferroni corrected level, but effect sizes remained medium to large. Effect sizes for the affective psychosis and psychotic experiences groups remained small. Group-by-age interactions for the non-affective psychosis group on performance IQ, digit symbol coding, digit span and sky search remained significant (Cohen $d \Delta=-0.64$, $p=.002$; Cohen $d \Delta=-0.73$, $p=.001$; Cohen $d \Delta=-0.65$, $p=.006$; Cohen $d \Delta=-0.57$, $p<.001$, respectively).

Adjusting for other neuropsychological tests

Main effects for the non-affective psychosis group on vocabulary and block design were no longer statistically significant at the Bonferroni level when adjusting for all other neuropsychological tests (**Table 3.6**)(Cohen $d=-0.71$, $p=.04$; Cohen $d=-0.37$, $p=.1$, respectively). Group-by-age interactions for the non-affective psychosis group on digit symbol coding, digit span and sky search remained statistically significant (Cohen $d \Delta=-0.82$, $p=.001$; Cohen $d \Delta=-0.70$, $p=.005$; Cohen $d \Delta=-0.50$, $p<.001$ respectively).

Figure 3.7 Scores and effect sizes by group at ages 8 and 20

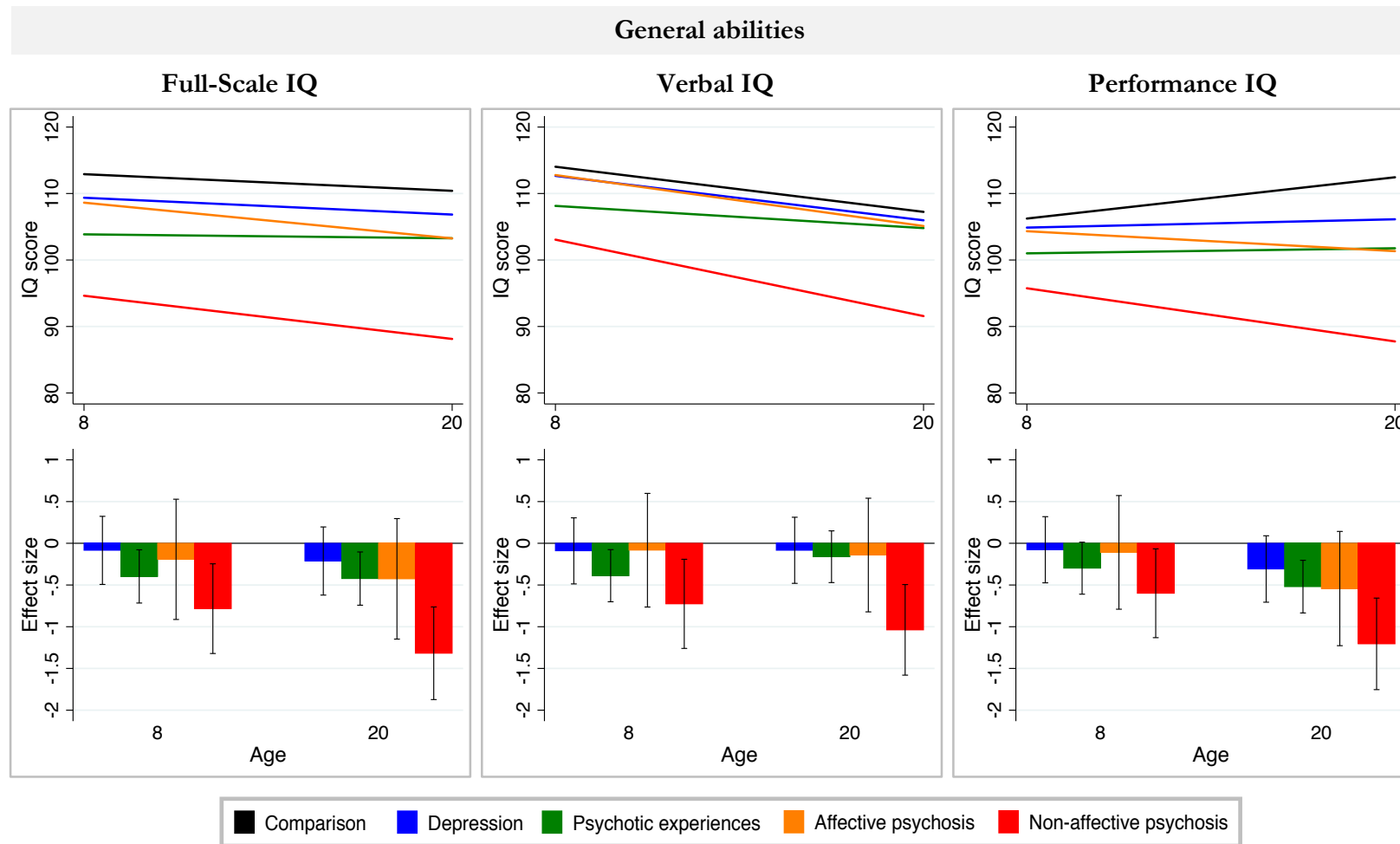


Figure 3.7 (continued) Scores and effect sizes by group at ages 8 and 20

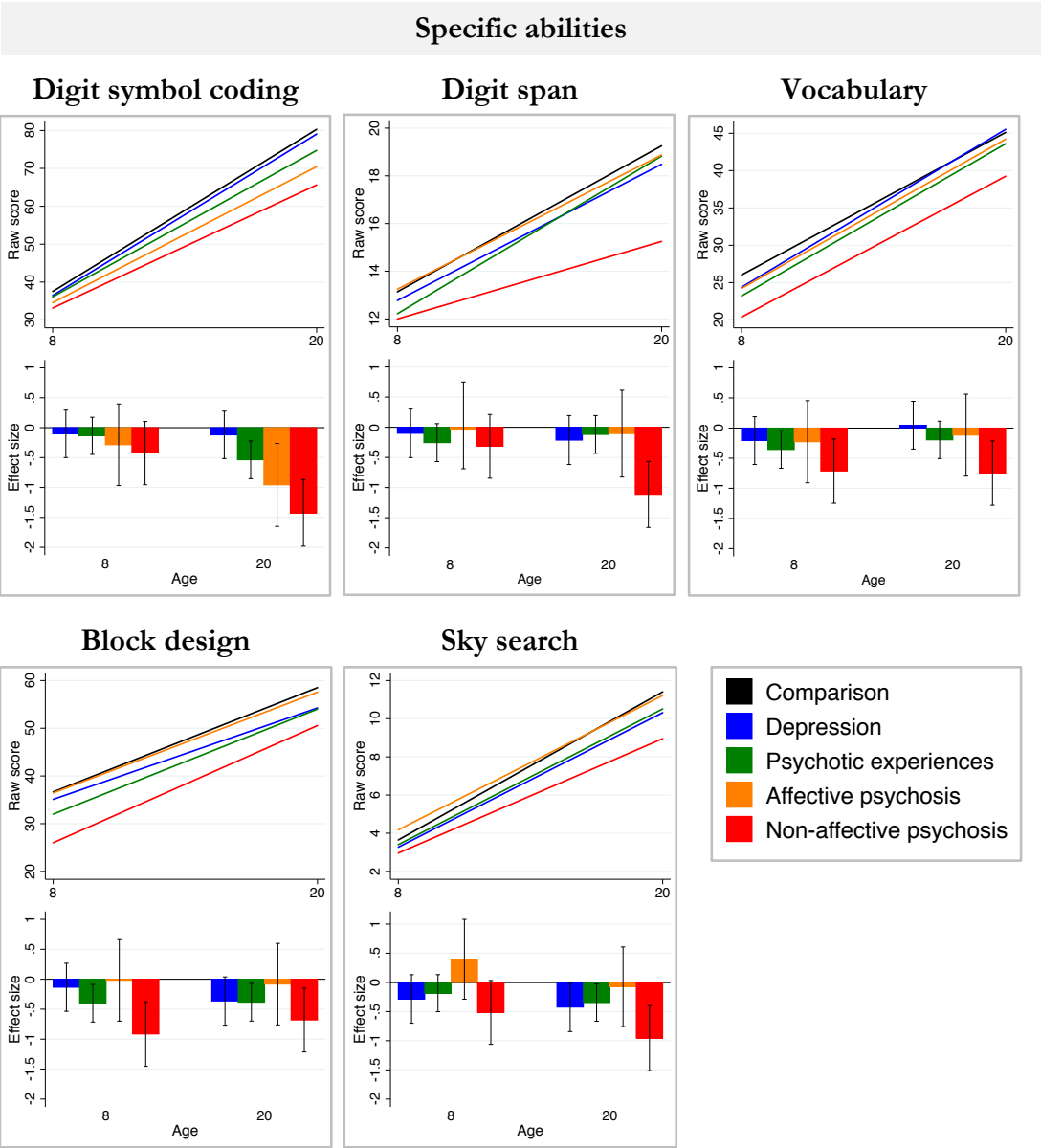


Table 3.6 Group and group-by-age interaction effects of multilevel random regression analysis on cognitive measures at ages 8 and 20 years*

	Control N=106	Non-affective psychosis N=16					Affective psychosis N=9				
Group effect	\bar{x}	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size
Full-scale IQ	111.0	93.8	-12.25	4.25	.004	-1.17	105.9	-3.00	5.79	.6	-0.34
Verbal IQ	110.6	97.3	-10.97	4.09	.007	-0.99	108.9	-1.25	5.29	.8	-0.13
Performance IQ	109.3	91.8	-10.48	4.74	.03	-1.03	102.8	-1.90	4.74	.8	-0.38
Digit symbol coding	58.9	49.4	-4.38	2.21	.05	-1.11	55.4	-2.95	2.85	.3	-0.74
Digit span	16.2	13.6	-1.14	0.81	.1	-0.83	16.1	0.11	1.11	.9	-0.04
Forward	8.5	7.4	-0.18	0.36	.6	-0.73	8.5	0.32	0.49	.5	0
Backward	5.6	4.4	-0.44	0.35	.2	-0.79	5.5	-0.12	0.47	.8	-0.09
Vocabulary	35.6	29.8	-5.64	2.00	.005	-0.87	34.2	-1.80	2.60	.5	-0.20
Block design	47.6	38.3	-10.66	3.16	.001	-0.90	47.0	-0.22	4.08	.9	-0.06
Sky search	7.5	6.0	-0.69	0.37	.07	-0.87	7.7	0.53	0.47	.3	0.09
Selective	4.8	3.9	-0.12	0.27	.7	-0.71	4.8	0.23	0.35	.5	-0.03
Sustained	2.7	2.1	-0.60	0.16	<.001	-0.96	2.9	0.32	0.21	.1	-0.33
Group-by-age effect	$\bar{x}\Delta$	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ
Full-scale IQ	-1.2	-11.3	-10.03	3.60	.005	-0.54	-5.4	-4.15	4.91	.4	-0.23
Verbal IQ	-6.8	-11.5	-4.71	3.77	.2	-0.31	-7.7	-0.88	4.87	.9	-0.06
Performance IQ	6.2	-8.0	-14.21	4.52	.002	-0.61	-3.0	-9.21	5.85	.1	-0.43
Digit symbol coding	42.8	32.5	-10.31	3.06	.001	-0.68	35.9	-6.92	3.96	.08	-0.45
Digit span	6.1	3.3	-2.87	0.99	.004	-0.59	5.6	-0.49	1.35	.7	-0.13
Forward	6.4	4.5	-1.89	0.52	<.001	-0.81	5.8	-0.64	0.71	.4	-0.39
Backward	4.0	2.4	-1.60	0.50	.001	-0.57	4.0	-0.04	0.68	.9	0.03
Vocabulary	19.1	18.9	-0.23	2.36	.9	0.07	20.0	0.89	3.05	.8	0.14
Block design	21.8	24.6	2.71	2.90	.3	0.23	21.1	-0.74	3.75	.8	-0.06
Sky search	7.8	6.0	-1.76	0.55	.001	-0.44	7.0	-0.72	0.69	.3	-0.47
Selective	5.2	3.6	-1.58	0.39	<.001	-0.81	4.7	-0.53	0.51	.3	-0.40
Sustained	2.5	2.4	-0.10	0.24	.7	0.29	2.4	-0.19	0.30	.5	-0.46
Psychotic experiences N=65						Depression N=32					
Group effect	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size	
Full-scale IQ	104.3	-6.23	2.54	.01	-0.45	108.6	-1.33	3.29	.7	-0.17	
Verbal IQ	106.5	-5.89	2.41	.01	-0.31	109.3	-1.37	3.08	.7	-0.13	
Performance IQ	101.4	-5.23	2.79	.06	-0.46	105.5	-1.36	3.57	.7	-0.22	
Digit symbol coding	55.4	-1.41	1.30	.3	-0.40	57.8	-1.07	1.66	.5	-0.13	
Digit span	15.5	-0.84	0.48	.08	-0.22	15.6	-0.36	0.62	.6	-0.18	
Forward	8.2	-0.23	0.21	.3	-0.20	7.9	-0.31	0.27	.3	-0.40	
Backward	5.4	-0.22	0.20	.3	-0.13	5.8	0.18	0.26	.5	0.07	
Vocabulary	33.4	-2.82	1.18	.01	-0.33	35.0	-1.64	1.51	.3	-0.09	
Block design	43.0	-4.68	1.87	.01	-0.44	44.7	-1.57	2.41	.5	-0.28	
Sky search	7.0	-0.25	0.22	.3	-0.32	6.8	-0.38	0.37	.2	-0.41	
Selective	4.5	-0.03	0.16	.8	-0.23	4.4	-0.08	0.21	.7	-0.31	
Sustained	2.4	-0.20	0.10	.04	-0.39	2.4	-0.27	0.12	.03	-0.45	
Group-by-age effect	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ	
Full-scale IQ	-2.1	-0.90	2.15	.7	-0.03	-3.5	-2.24	2.79	.4	-0.13	
Verbal IQ	-3.3	3.45	2.22	.1	0.23	-6.7	0.10	2.84	.9	0.01	
Performance IQ	0.8	-5.44	2.67	.04	-0.22	-1.3	-4.96	3.41	.1	-0.23	
Digit symbol coding	38.7	-4.14	1.81	.02	-0.29	42.6	-0.18	2.31	.9	0.03	
Digit span	6.6	0.49	0.59	.4	0.20	5.7	-0.41	0.75	.6	-0.07	
Forward	6.2	-0.15	0.31	.6	0	5.8	-0.62	0.39	.1	-0.19	
Backward	4.1	0.04	0.30	.9	0.09	3.9	-0.14	0.38	.7	-0.12	
Vocabulary	20.4	1.29	1.39	.4	0.21	21.2	2.05	1.77	.2	0.28	
Block design	22.0	0.19	1.71	.9	0.02	19.2	-2.68	2.21	.2	-0.23	
Sky search	7.1	-0.65	0.32	.04	-0.16	7.1	-0.71	0.42	.08	-0.14	
Selective	4.7	-0.51	0.23	.03	-0.27	4.6	-0.64	0.31	.04	-0.31	
Sustained	2.4	-0.13	0.14	.3	0.01	2.5	-0.08	0.18	.6	0.09	

*Results in bold signify $p < .008$

Table 3.6 (continued) Group and group-by-age interaction effects of multilevel random regression analysis on cognitive measures at ages 8 and 20 years adjusting for confounders*

	Control N=100	Non-affective psychosis N=15					Affective psychosis N=9				
Group effect	\bar{x}	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size
Full-scale IQ	110.0	96.1	-9.09	4.32	.03	-0.96	110.2	2.11	6.38	.7	0.01
Verbal IQ	109.9	99.1	-8.80	4.13	.03	-0.83	111.7	2.22	5.99	.7	0.14
Performance IQ	108.2	94.5	-6.59	4.79	.1	-0.82	106.5	2.65	7.09	.7	-0.10
Digit symbol coding	58.9	49.1	-4.40	2.32	.06	-1.15	50.9	-4.37	3.35	.2	-0.92
Digit span	16.0	14.1	-0.56	0.85	.5	-0.65	16.6	0.89	1.24	.5	-0.20
Forward	8.5	7.4	-0.11	0.38	.8	-0.72	8.6	0.45	0.56	.4	0.06
Backward	5.6	4.6	-0.28	0.38	.4	-0.67	5.6	-0.06	0.56	.9	-0.05
Vocabulary	35.2	31.4	-3.59	2.09	.09	-0.59	34.4	-1.11	2.96	.7	-0.12
Block design	46.3	40.9	-6.71	3.27	.04	-0.53	52.1	5.95	4.65	.2	0.56
Sky search	7.5	5.9	-0.61	0.40	.1	-0.90	7.3	0.16	0.56	.8	-0.13
Selective	4.8	3.9	-0.07	0.29	.8	-0.71	4.6	0.08	0.43	.9	-0.16
Sustained	2.7	2.0	-0.54	0.17	.002	-0.96	2.7	0.10	0.25	.7	-0.02
Group-by-age effect	$\bar{x}\Delta$	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ
Full-scale IQ	-1.5	-11.1	-9.55	3.73	.01	-0.54	-5.4	-3.86	4.94	.4	-0.24
Verbal IQ	-6.8	-10.8	-3.99	3.90	.3	-0.27	-7.7	-0.86	4.91	.9	0.23
Performance IQ	5.6	-8.5	-14.22	4.68	.002	-0.64	-3.0	-8.69	5.88	.1	-0.45
Digit symbol coding	43.0	32.3	-10.75	3.17	.001	-0.73	35.9	-7.13	3.98	.07	-0.43
Digit span	6.2	3.4	-2.79	1.02	.006	-0.65	5.6	-0.57	1.36	.7	-0.22
Forward	6.5	4.5	-1.99	0.52	<.001	-0.89	5.8	-0.71	0.69	.3	-0.45
Backward	4.0	2.5	-1.57	0.52	.003	-0.61	4.0	-0.03	0.69	.9	0.01
Vocabulary	19.4	19.0	-0.37	2.42	.9	-0.01	20.0	0.63	3.04	.8	0.09
Block design	21.5	24.1	2.57	3.02	.4	0.23	21.1	-0.38	3.80	.9	-0.03
Sky search	7.8	5.8	-1.99	0.55	<.001	-0.57	7.0	-0.80	0.68	.2	-0.36
Selective	5.3	3.6	-1.66	0.41	<.001	-0.89	4.7	-0.57	0.51	.3	-0.34
Sustained	2.6	2.4	-0.21	0.24	.4	0.13	2.4	-0.23	0.29	.4	-0.30
Psychotic experiences N=63						Depression N=29					
Group effect	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size	
Full-scale IQ	105.1	-4.32	2.53	.09	-0.34	110.0	0.53	3.36	.9	0	
Verbal IQ	107.4	-4.03	2.38	.09	-0.19	111.7	1.66	3.14	.6	0.14	
Performance IQ	101.5	-4.01	2.76	.1	-0.40	106.0	-0.50	3.63	.9	-0.13	
Digit symbol coding	55.4	-1.25	1.31	.3	-0.41	57.3	-1.19	1.73	.5	-0.18	
Digit span	15.5	-0.75	0.48	.1	-0.16	15.9	-0.06	0.65	.9	-0.04	
Forward	8.2	-0.19	0.22	.4	-0.18	8.0	-0.26	0.29	.4	-0.29	
Backward	5.4	-0.22	0.22	.3	-0.13	5.8	0.23	0.29	.4	-0.12	
Vocabulary	33.8	-2.09	1.19	.08	-0.23	35.8	-0.42	1.57	.8	0.10	
Block design	43.0	-3.58	1.87	.06	-0.33	45.8	0.33	2.48	.9	-0.05	
Sky search	7.0	-0.16	0.22	.5	-0.31	6.6	-0.41	0.30	.2	-0.50	
Selective	4.5	0.01	0.17	.9	-0.23	4.3	-0.06	0.23	.8	-0.36	
Sustained	2.5	-0.15	0.10	.1	-0.35	2.3	-0.28	0.13	.03	-0.52	
Group-by-age effect	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ	
Full-scale IQ	-2.7	-1.14	2.21	.6	-0.05	-2.5	-1.00	2.93	.7	-0.06	
Verbal IQ	-3.8	3.03	2.27	.1	0.20	-6.4	0.36	2.98	.9	0.03	
Performance IQ	0.3	-5.41	2.73	.04	-0.23	2.3	-3.38	3.57	.3	-0.16	
Digit symbol coding	38.6	-4.47	1.85	.02	-0.34	42.3	-0.74	2.42	.8	-0.02	
Digit span	6.7	0.53	0.60	.4	0.21	6.1	-0.08	0.79	.9	-0.02	
Forward	6.3	-0.17	0.31	.6	-0.02	6.1	-0.35	0.40	.4	-0.09	
Backward	4.1	0.05	0.31	.8	0.10	4.0	-0.07	0.41	.9	-0.11	
Vocabulary	20.6	1.26	1.41	.3	0.18	21.4	2.08	1.85	.3	0.26	
Block design	22.0	0.46	1.77	.8	0.04	19.8	-1.71	2.34	.5	-0.32	
Sky search	7.1	-0.78	0.32	.01	-0.25	6.9	-0.96	0.43	.03	-0.24	
Selective	4.6	-0.61	0.24	.01	-0.33	4.4	-0.82	0.32	.01	-0.42	
Sustained	2.4	-0.18	0.14	.2	-0.09	2.4	-0.15	0.18	.4	0.03	

*Results in bold signify $p < .008$

Table 3.6 (continued) Group and group-by-age interaction effects of multilevel random regression analysis on cognitive measures at ages 8 and 20 years adjusting for other cognitive measures*

	Control N=95	Non-affective psychosis N=15					Affective psychosis N=8				
Group effect	\bar{x}	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size
Digit symbol coding	58.4	50.7	-2.44	2.32	.3	-0.95	52.2	-2.33	2.98	.4	-0.77
Digit span	15.9	14.2	-0.30	0.84	.7	-0.58	16.5	0.68	1.08	.5	0.17
Forward	8.4	7.6	0.09	0.38	.8	-0.56	8.6	0.46	0.49	.4	0.11
Backward	5.5	4.5	-0.28	0.35	.4	-0.71	5.6	-0.01	0.46	.9	0.05
Vocabulary	35.5	30.9	-4.37	2.14	.04	-0.71	33.8	-2.24	2.74	.4	-0.27
Block design	46.5	43.0	-4.54	3.12	.2	-0.37	48.3	1.99	4.01	.6	-0.19
Sky search	7.5	6.0	-0.62	0.38	.1	-0.86	7.6	0.51	0.49	.3	0.59
Selective	4.8	3.9	-0.09	0.28	.7	-0.72	4.7	0.19	0.36	.6	-0.07
Sustained	2.7	2.1	-0.49	0.17	.004	-0.81	2.9	0.38	0.22	.9	0.37
Group-by-age effect	$\bar{x}\Delta$	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ
Digit symbol coding	42.2	31.7	-10.51	3.22	.001	-0.82	34.5	-7.74	4.26	.07	-0.59
Digit span	6.0	3.1	-2.83	1.02	.005	-0.70	5.6	-0.34	1.35	.8	-0.15
Forward	6.3	4.5	-1.88	0.53	<.001	-0.90	5.8	-0.60	0.71	.4	-0.41
Backward	3.8	2.3	-1.57	0.49	.002	-0.64	4	0.16	0.66	.8	0.08
Vocabulary	19.1	18.5	-0.56	2.48	.8	-0.01	20.1	1.03	3.28	.8	0.15
Block design	21.7	23.8	2.10	3.06	.5	0.19	21.3	-0.45	4.06	.9	-0.04
Sky search	7.8	6.0	-1.80	0.54	.001	-0.50	7.0	-0.81	0.71	.3	-0.51
Selective	5.2	3.6	-1.60	0.38	<.001	-0.86	4.7	-0.56	0.52	.3	-0.40
Sustained	2.6	2.4	-0.11	0.24	.6	0.20	2.3	-0.26	0.31	.4	-0.51
Psychotic experiences N=61						Depression N=28					
Group effect	\bar{x}	β	SE	p	Effect size	\bar{x}	β	SE	p	Effect size	
Digit symbol coding	55.6	-0.83	1.35	.5	-0.34	58.1	-0.44	1.78	.5	-0.04	
Digit span	15.7	-0.60	0.49	.2	-0.07	15.6	-0.33	0.64	.6	-0.12	
Forward	8.2	-0.17	0.22	.5	-0.11	7.9	-0.30	0.29	.3	-0.35	
Backward	5.5	-0.15	0.21	.5	-0.01	5.8	0.11	0.27	.7	0.15	
Vocabulary	33.4	-2.49	1.24	.05	-0.33	35.8	-0.80	1.63	.6	0.05	
Block design	43.3	-3.23	1.82	.08	-0.34	45.3	-0.02	2.38	.9	-0.01	
Sky search	6.9	-0.17	0.22	.4	-0.33	6.8	-0.35	0.29	.2	-0.41	
Selective	4.5	-0.01	0.16	.9	-0.28	4.4	-0.08	0.22	.7	-0.32	
Sustained	2.5	-0.13	0.10	.1	-0.30	2.4	-0.24	0.13	.07	-0.44	
Group-by-age effect	$\bar{x}\Delta$	β	SE	p	Effect size Δ	$\bar{x}\Delta$	β	SE	p	Effect size Δ	
Digit symbol coding	38.4	-3.81	1.91	.05	-0.30	42.5	0.28	2.53	.9	0.04	
Digit span	6.8	0.79	0.60	.9	0.25	5.9	-0.04	0.80	.9	0.02	
Forward	6.3	0	0.32	.9	0.05	5.9	-0.46	0.42	.3	-0.13	
Backward	4.1	0.28	0.29	.3	0.18	4.1	0.24	0.39	.5	0.07	
Vocabulary	19.8	0.74	1.47	.6	0.12	21.3	2.20	1.95	.3	0.28	
Block design	21.8	0.09	1.82	.9	-0.01	19.3	-2.40	2.41	.3	-0.22	
Sky search	7.0	-0.83	0.32	.01	-0.27	7.0	-7.45	0.42	.08	-0.17	
Selective	4.6	-0.68	0.23	.004	-0.38	4.6	-0.63	0.31	.04	-0.32	
Sustained	2.4	-0.15	0.14	.3	-0.07	2.4	-0.12	0.18	.5	0.03	

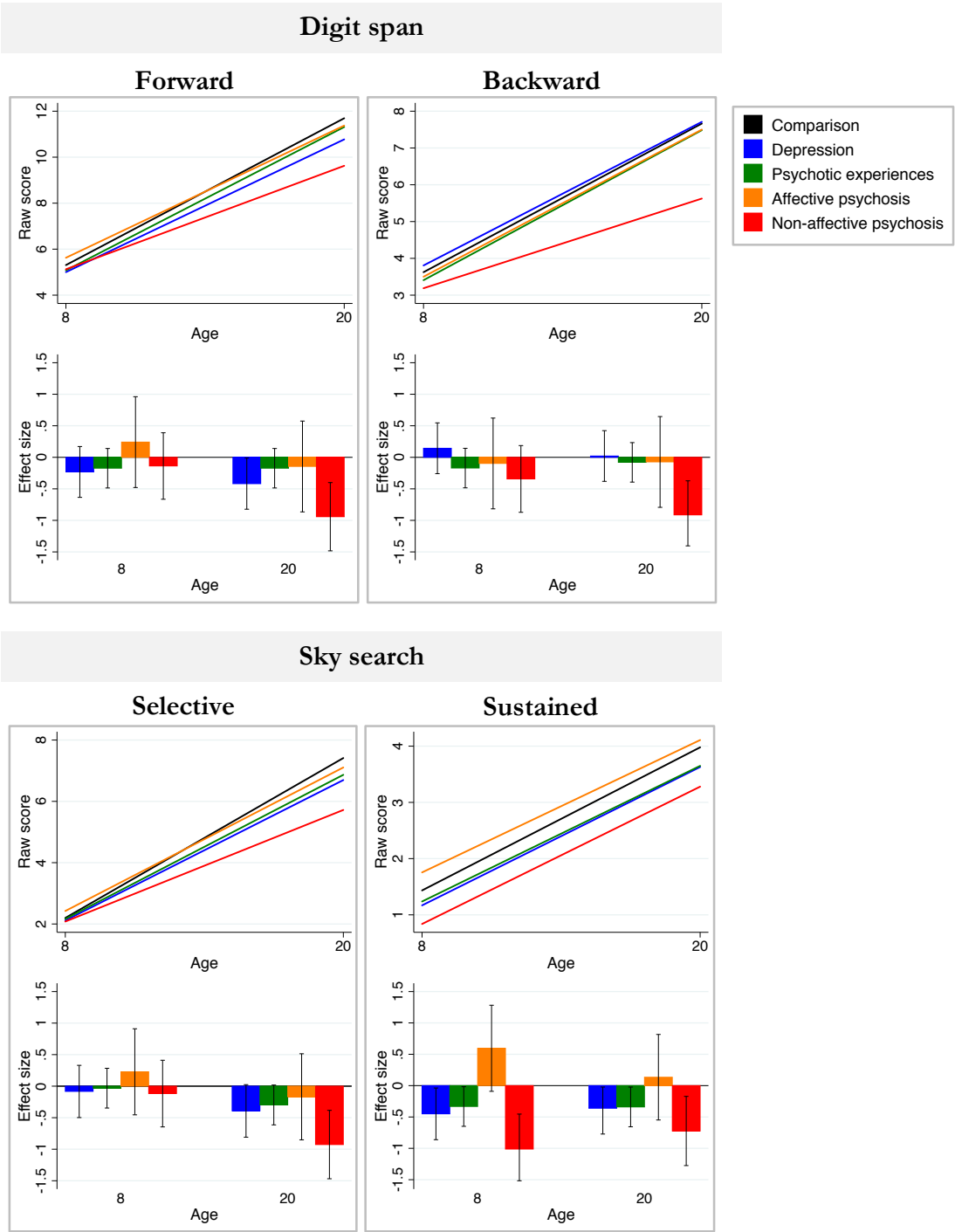
*Results in bold signify $p < .008$

Digit span and sky search subcomponents

We further examined the digit span and sky search tasks by dividing them into their subcomponents. **Figure 3.8** shows raw scores and effect sizes for the forward and backward components of the digit span, and the selective and sustained components of the sky search. Group-by-age interactions were significant for the non-affective psychosis group on both components of the digit span (Cohen $d \Delta = -0.81, p < .001$ and Cohen $d \Delta = -0.57, p = .001$ respectively) and on the selective sky search task (Cohen $d \Delta = -0.81, p < .001$), suggesting developmental lags. There was a main effect for the non-affective psychosis group on the sustained sky search task (Cohen $d = -0.96, p < .001$), suggesting a static deficit. Main effects on the sustained sky search for the depression and psychotic experiences groups did not reach Bonferroni corrected significance (Cohen $d = -0.45, p = .03$ and Cohen $d = -0.39, p = .04$). Similarly, group-by-age interactions on the selective sky search task for the psychotic experiences and depression groups were not significant after Bonferroni correction (Cohen $d \Delta = -0.31, p = .04$ and Cohen $d \Delta = -0.27, p = .03$ respectively). Group-by-age interactions for the non-affective psychosis group on the forward and backward components of the digit span (Cohen $d \Delta = -0.89, p < .001$ and Cohen $d \Delta = -0.61, p = .003$ respectively) and on the selective sky search task (Cohen $d \Delta = -0.89, p < .001$), remained statistically significant after adjusting for confounders, as did the main effect for the non-affective psychosis group on the sustained sky search task (Cohen $d = -0.96, p = .002$) (**Table 3.4**). Group-by-age interactions for the non-affective psychosis group on the forward and backward components of the digit span (Cohen $d \Delta = -0.90, p < .001$ and Cohen $d \Delta = -0.64, p = .002$ respectively) and on the selective sky search task (Cohen $d \Delta = -0.86, p < .001$), remained statistically significant after adjusting for all other neuropsychological

tests, as did the main effect for the non-affective psychosis group on the sustained sky search task (Cohen $d=-0.81, p=.004$) (Table 3.4).

Figure 3.8 Raw scores and effect sizes by diagnostic group at ages 8 and 20 for digit span and sky search subtasks



Discussion

By using a population-based cohort followed prospectively from birth, this study provides the strongest evidence to date of IQ decline between childhood and adulthood in individuals with non-affective psychosis. This finding is in line with previous longitudinal studies of childhood neuropsychological functioning in individuals who go on to develop schizophrenia (Reichenberg et al., 2010; Meier et al., 2013; MacCabe et al., 2013).

Our findings advance knowledge in several ways. First, we traced the course of IQ through infancy, childhood, adolescence and early adulthood. The non-affective psychosis group showed increasing full-scale and performance IQ deficits during two developmental periods: 1) from infancy to childhood and 2) from adolescence to early adulthood. This group also showed an increasing verbal IQ impairment during infancy, followed by relative stabilization through adolescence and early adulthood. Importantly, our findings suggest that those who develop psychosis may experience decline, not only in fluid abilities (e.g. working memory), but also crystallized abilities (e.g. verbal IQ), albeit during different developmental periods.

Cognitive deficits in schizophrenia have been hypothesized to be the product of two developmental processes: 1) static deficit and 2) increasing lag (Reichenberg et al., 2010). However, previous studies have been limited by the developmental periods during which data were available, with only few studies spanning late childhood and early adolescence (Reichenberg et al., 2010; Gochman et al., 2005) and even fewer in early childhood and late adolescence (Agnew-Blais et al., 2015; MacCabe et al., 2013).

Our findings, which span infancy (18 months) to early adulthood (20 years), suggest that the cognitive deficits associated with non-affective psychosis may be due to a single, dynamic process across cognitive functions. Specifically, increasing lags may be present across cognitive functions, with the largest lags seen during potentially critical developmental periods.

Second, we focused on the period encompassing adolescence (age 8 to 20) using identical measures of general and specific neuropsychological functions across ages. Cognitive developmental growth was ubiquitous across groups and neuropsychological functions. The rate of growth, however, differed between functions and groups, especially the non-affective psychosis group. Slowed growth in processing speed, working memory and attention abilities led to increasing lags in these functions, while early deficits in language and visuospatial functions did not change over time. To the best of our knowledge, this is the first study to use identical neuropsychological tests administered over this developmental period, one hypothesized to be of critical risk for schizophrenia (Weinberger, 1987; Murray and Lewis, 1987). Importantly, our findings suggest that cognitive decline in schizophrenia is due, not to an absolute loss or deterioration in cognition over time, but rather to a failure to keep up with developmentally normal rates of cognitive growth.

Third, we compared neuropsychological functioning in non-affective psychosis to subclinical psychotic experiences, affective psychosis and depression. The psychotic experiences group showed small, static full-scale and verbal IQ, and language and visuospatial deficits. Small processing speed lags were also seen in the psychotic experiences and affective psychosis groups, and the psychotic experiences group

showed an additional attention lag. The depression group showed small, increasing deficits in full-scale and performance IQ. However, only the non-affective psychosis group showed large, statistically significant cognitive deficits after Bonferroni correction. Moreover, the magnitude of impairments in non-affective psychosis was substantially greater than in the other groups. Indeed, the size of impairments seen here at age 20 matches that of first episode and chronic schizophrenia patients (Mesholam-Gately et al., 2009; Reichenberg and Harvey, 2007). Previous findings regarding the specificity of cognitive deficits to psychosis are mixed, with reports of small, stable deficits across cognitive domains in depression (Meier et al., 2013; Reichenberg et al., 2010), verbal IQ decline in affective psychosis (MacCabe et al., 2013) and processing speed delays in psychotic experiences (Niarchou et al., 2013). Our findings suggest that large, increasing impairments, across general and specific, fluid and crystallized cognitive abilities are specific to clinical, non-affective psychotic disorder. Interestingly, the affective psychosis group outperformed the non-affective psychosis group across all cognitive functions, but also showed only small deficits compared to controls on all domains, except processing speed. Similar findings have been reported on IQ (Agnew-Blais et al., 2015) and specific functions (Lewandowski et al., 2013; Quide et al., 2016). One possible explanation is that psychotic disorders with and without accompanying affective symptoms have different etiologies (Murray et al., 2004). While affective and non-affective psychoses may share certain susceptibility genes (Purcell et al., 2009), additional genetic and/or environmental risk factors may lead to distinct neurodevelopmental profiles (Murray et al., 2004). For example, environmental stressors may predispose more to affective psychotic disorders accompanied by mild

cognitive impairment, while early neurodevelopmental insults may predispose more to non-affective psychotic disorders often accompanied by severe cognitive deficits.

Our findings have important theoretical and clinical implications. First, in non-affective psychosis, the extent and timing of cognitive deficits varied between functions.

Crystallized abilities (e.g. verbal IQ) may decline during infancy and remain relatively stable thereafter, while deficits in fluid abilities (e.g. working memory) may increase monotonically throughout childhood, adolescence and early adulthood. One possibility is that early neurodevelopmental insults may lead to deficits in verbal functions that develop in early life and interact with later neurodevelopmental processes, leading to increasing deficits in functions that mature later (Pantelis et al., 2003). Alternatively, verbal deficits emerging in early childhood may impede normal developmental growth in other cognitive functions, leading to increasing deficits during late adolescence and beyond. Clinically, our findings highlight the importance of early interventions for cognitive deficits. Crystallized abilities may be more amenable to change during childhood, while later interventions, possibly during adolescence, may be most effective for fluid abilities.

This study has some limitations. First, the analyses spanning infancy to early adulthood utilized variable numbers of individuals available at different ages and, at certain ages, only small groups with psychotic disorder. Thus, while our sample was drawn from a well-characterized, population-based, birth cohort, these findings require replication in independent samples. Nevertheless, the results of the longitudinal high-risk sample at ages 8 and 20 corroborate those from infancy to adulthood (**Appendix II, Figure 1**). Moreover, inspection of full-scale, verbal and performance IQ in individuals with data

available at all time points provides further support for increasing deficits (**Figure 3.6**). Aggregating the affective and non-affective psychosis groups at ages 18 months and 4 years due to small cell counts also resulted in a similar pattern of results (**Appendix II, Figure 2**). Results using imputed data also did not differ substantially from those using unimputed data (**Appendix II, Figure 3**). Second, while we classified those comorbid for depression and psychotic experiences into the depression group, this group may have a distinct neuropsychological profile from those with depression and no psychotic experiences. However, supplemental analyses separating out this comorbid group suggest that they do not differ substantially or consistently across domains from those with depression or psychotic experiences alone (**Appendix II, Figures 4-7**).

Conclusions

Our findings suggest a distinct course of cognitive deficits in individuals with non-affective psychosis that is different to individuals with depression, but also subclinical psychotic experiences and affective psychosis. While all groups showed a degree of cognitive impairment, only the non-affective psychosis group showed progressively increasing deficits across multiple cognitive domains.

The Structure of Cognition in Childhood and Adulthood across the Psychosis Spectrum

Abstract

There is substantial evidence for connection abnormalities in the brains of schizophrenia patients. However, little is known about the structure of cognition across the psychosis spectrum. We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Data from all individuals who underwent cognitive testing at age 8 and psychiatric assessment at 18 years were used to examine network structure of cognition in childhood (age 8). A subsample of individuals who underwent further cognitive testing at age 20 was used to examine change in cognitive network structure between childhood (age 8) and adulthood (age 20). Networks comprised nodes (cognitive tests) joined together by edges (partial correlations). Organization of subnetworks by cognitive domains (verbal, perceptual, working memory and processing speed) and measures indicating 1) important cognitive tests or hubs, 2) network integration and 3) network density, were examined. Participants with non-affective psychotic disorder, affective psychotic disorder, psychotic experiences and depression were compared to controls. In childhood, affective and non-affective psychosis groups showed disruption to cognitive subnetworks and hubs, as well as greater network connectivity ($\beta=0.44, p<.001, \beta=0.16, p<.001$), dysconnectivity ($\beta=-0.47, p<.001, \beta=-0.19, p=.002$), integration ($\beta=-12.7, p<.001, \beta=-10.2, p<.001$) and density ($\beta=0.49, p<.001, \beta=0.17, p<.001$). The psychotic experiences group showed intact subnetworks and hubs, but increased network integration ($\beta=-5.5, p<.001$) and density ($\beta=0.02,$

$p=.04$). The depression group also showed intact subnetworks and hubs, but increased integration ($\beta=-5.9, p<.001$). Between childhood and adulthood increasing density was seen in the psychotic experiences group ($\beta=0.09, p=.04$), and the depression group showed increasing integration ($\beta=-3.15, p=.04$). Controls showed increasing reliance on the working memory hub between childhood and adulthood, while all other groups remained reliant on attention and visuospatial abilities. Overall, individuals with psychotic disorder showed substantial qualitative and quantitative differences in cognitive network structure. Individuals with psychotic experiences and depression showed more subtle deviations. Abnormalities in cognitive network structure were seen even in the absence of cognitive impairment, suggesting the importance of looking beyond deficits to how performance is achieved.

Introduction

Schizophrenia has been conceptualized as a disorder of brain dysconnectivity for decades (Friston and Frith, 1995). More recently, rapid advances in neuroscience and application of graph theory has led to a flurry of evidence that the brains of schizophrenia patients show structural and functional connection abnormalities (Fornito et al., 2012). Frontotemporal dysconnectivity has most consistently been reported, but findings of aberrant connectivity in parietal, temporal and occipital regions (Fornito et al., 2012) suggests disconnection at a global level. In line with imaging findings, the cognitive deficits in schizophrenia have been characterized as specific impairments, such as in working memory and executive functions, superimposed on a general IQ deficit (Reichenberg and Harvey, 2007). Abnormalities in network organization, integration and density have also been reported (Griffa et al.,

2013), yet the exact nature of these abnormalities remains contested (Fornito et al., 2012; Drakesmith et al., 2015). Moreover, while a recent meta-analysis suggested that network topology is related to cognitive function in healthy brains (Crossley et al., 2013), little is known about how anomalies in brain connectivity are related to cognition in schizophrenia.

Studies on the structure of cognition have invariably found evidence for a general underlying factor, or *g*. The differentiation hypothesis of cognition (Spearman, 1927) proposes that *g* varies with age and ability, such that *g* strength decreases with increasing age and increasing ability (Van Der Maas et al., 2006). Evidence for both phenomena is mixed, with findings in support (Abad et al., 2003; Deary et al., 1996), but also against (Fogarty and Stankov, 1995), ability differentiation, as well as age differentiation (Tideman and Gustafsson, 2004; Bickley et al., 1995; Juan-Espinosa et al., 2000). Methodological limitations may partly account for inconsistencies in findings (Van Der Maas et al., 2006). Another plausible explanation is that the association between age and *g* strength is nonlinear, changing over the course of the life span. The dedifferentiation hypothesis (Deary et al., 2004; Lienert and Crott, 1964) posits an increase in *g* strength with age and has mostly been applied to the investigation of cognitive aging, which may begin as early as young adulthood (Lienert and Crott, 1964; Salthouse, 2009) and accelerate in late adulthood (Craik and Bialystok, 2006). Differentiation may occur through childhood and adolescence (Lienert and Crott, 1964), but dedifferentiation has been reported between adolescence and adulthood (Lienert and Crott, 1964), and more strikingly, between late and very late adulthood (Deary et al., 2004).

Recent factor analytic studies provide initial insight into the structure of cognition in schizophrenia (Nuechterlein et al., 2004). Studies have reported increased *g* strength, or dedifferentiation, in patients compared to controls (Haring et al., 2015; Dickinson et al., 2006; Strauss and Summerfelt, 2003), while others have reported negligible group differences (Gladysjo et al., 2004). On the one hand, dedifferentiation suggests that cognitive functioning in schizophrenia may rely more on a unitary construct and less on domain specific processes (Dickinson et al., 2004), in line with generalized deficit models of cognition in schizophrenia. However, a review of factor analytic studies in schizophrenia concluded that ‘multiple independent or only weakly correlated factors’ may best account for variations in cognitive performance (Nuechterlein et al., 2004). Thus, the factor structure of cognition in schizophrenia patients remains contested.

The use of factor analysis to investigate the structure of cognition has limitations. First, factor analysis usually requires large numbers of participants (Goekoop et al., 2012), which are generally not available in schizophrenia samples due to its low prevalence (McGrath et al., 2008). Second, associations between cognitive tests are not modelled during factor analysis. Yet, these associations may provide important information about structure since certain cognitive tests may, for example, be associated with few or many other cognitive tests, and have weaker or stronger associations (Goekoop et al., 2012). In network analysis, variables (e.g. cognitive tests) are plotted as individual nodes linked by edges (measures of association). Associations between variables (nodes) can be comprehensively examined and indices of centrality (importance) and clustering (integration) of nodes in the network can also be computed. Finally, a clear advantage over factor analysis is that associations between variables can be plotted visually so that the size, shape and density of networks can easily be discerned. Network analysis has

been used extensively in imaging research (Bullmore and Sporns, 2009) and more recently in studies on psychopathology (Isvoranu et al., 2016; Wigman et al., 2016) and personality (Costantini et al., 2015), but not, to our knowledge, to examine the structure of cognitive functioning.

We used data from an on-going population representative longitudinal study (the Avon Longitudinal Study of Parents and Children (Boyd et al., 2013; Fraser et al., 2013)) to examine the network structure of cognitive functioning in childhood (age 8).

Topological abnormalities have been associated with subclinical psychotic experiences in this sample (Drakesmith et al., 2015), but network analysis has not, to our knowledge, been applied to cognitive data across the psychosis spectrum. Moreover, dedifferentiation has been implicated in age-associated cognitive decline (Deary et al., 2004) and it would be interesting to investigate whether the cognitive decline described in the previous chapter is associated with changes in cognitive network structure. Thus, we used identical measures of processing speed, working memory, attention, language and visuospatial ability to assess changes in network structure between childhood (age 8) and adulthood (age 20). Subjects with non-affective psychotic disorder, affective psychotic disorder, subclinical psychotic experiences and depression were compared to control participants. We hypothesized that individuals with non-affective psychotic disorder would show subtle aberrations in cognitive network structure in childhood (age 8), as well as abnormal changes between childhood and adulthood (age 20). We hypothesized that individuals with affective psychotic disorder and psychotic experiences would show milder deviations in cognitive network structure.

Methods

Sample

The sample comprised individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (see pages 46-47).

Network structure of cognition in childhood

A total of 7,488 children underwent neuropsychological assessment at the age 8 assessment wave. Of these individuals, 3,930 also attended the age 18 assessment wave and underwent diagnostic interviewing. All 3,930 individuals with available age 8 cognitive data and age 18 diagnostic data were included in the analyses examining the network structure of cognition in childhood (age 8)(see page 47 and **Figure 3.1**).

Change in network structure of cognition between childhood and early adulthood

The high-risk longitudinal sample, comprising all individuals with age 8 and age 20 cognitive data and age 18 diagnostic data (see page 49 and **Figure 3.2**), was used to examine change in network structure of cognition between childhood (age 8) and early adulthood (age 20).

Measures

Psychotic experiences (PEs) and psychotic disorder

The semi-structured PLIKSi was used at age 18 to ascertain individuals with psychotic experiences and psychotic disorders (see pages 50-51).

Depression

Depression was measured at age 18 using the computerized version of the Clinical Interview Schedule–Revised (CIS-R)(Lewis et al., 1992)(see page 51).

Neuropsychological functioning

Trained psychologists administered all neuropsychological tests. The Wechsler Intelligence Scale for Children, 3rd edition (WISC-III)(Wechsler, 1991)(**Table 3.2**), as well as the Tests of Everyday Attention for Children (TEA-Ch)(Robertson et al., 1996) were administered at age 8. Identical versions of the digit symbol coding, digit span, vocabulary and block design subtests of the WISC-III, as well as the sky search task from the TEA-Ch (Robertson et al., 1996), were administered at age 20.

Statistical analysis

Our analyses compared five, mutually exclusive groups based on clinical interviews at age 18: 1) non-affective psychosis (psychotic disorder), 2) affective psychosis (comorbid for psychotic disorder and depression), 3) psychotic experiences, 4) depression and 5) healthy controls. Participants comorbid for psychotic experiences and depression were assigned to the depression group.

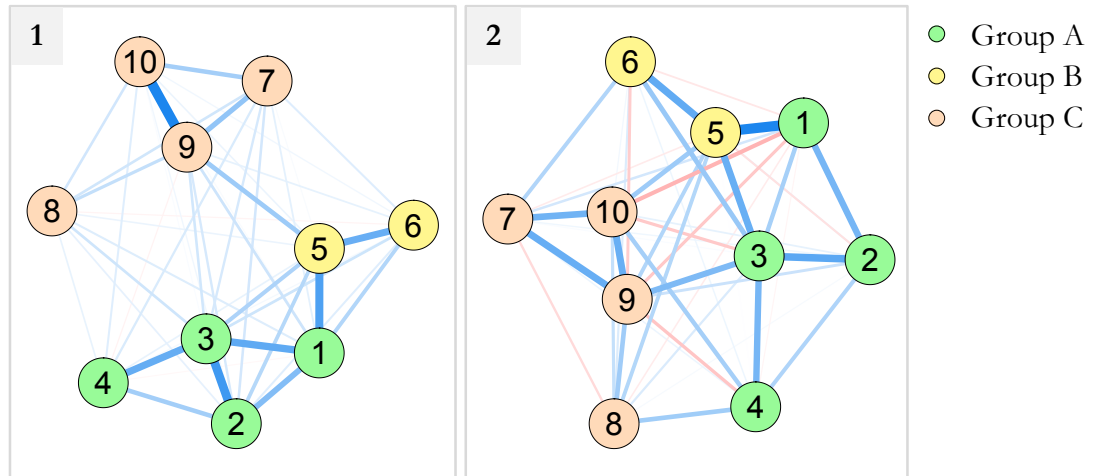
The R-package qgraph (Epskamp et al., 2011) was used to examine the network structure of cognitive functioning. Networks consist of nodes, which are linked together by edges. Edges can be unweighted i.e. showing presence or absence of an association, or weighted i.e. representing the strength of the association. In the present study the nodes represented each of the cognitive subtests. Partial correlations were used as the measure of association (edges) to link these nodes. Partial correlations give

the strength and direction of an association between two variables whilst controlling for the effect of other variables. The advantage of using partial correlations over correlations is that spurious associations between two variables, arising due to their shared association with a third variable, are avoided. In all network visualizations presented herein blue edges denote positive associations and red edges denote negative associations. The strength of these partial correlations is indicated by edge thickness, with thicker edges representing stronger associations and thinner edges representing weaker associations. In the interest of displaying parsimonious networks, edges (partial correlations) between -0.1 and 0.1 were not shown. Two examples of networks are visualized and described in **Figure 4.1**.

Several indices are useful in the interpretation of networks. The importance of a node to the network can be determined by computing various measures of node **centrality**. **Strength centrality** is computed using the sum of the weights of the edges adjacent to the node of interest. A node with high strength has more and stronger associations than a node with low strength and therefore, can influence or be influenced by other nodes directly. Network analysis also draws upon the concept of distance, which is defined as the shortest path length between two nodes. The **shortest path length**, in turn, is the path with the smallest number of edges. In weighted networks shortest path lengths are computed by first converting weights to lengths (Opsahl et al., 2010). Average shortest path length is an index of integration of the network, with shorter path lengths indicating greater integration. **Betweenness centrality** is the number of shortest path lengths between any two nodes that pass through the node of interest. A node with high betweenness lies on several shortest paths between other nodes in the network. Nodes with high betweenness centrality are closer to other nodes in the network than

nodes with low betweenness centrality. The 'centrality_auto' function was used to compute strength and betweenness centrality, and shortest path lengths.

Figure 4.1 Two examples of networks 1 and 2*



*Both networks have 10 nodes (numbered 1 to 10) and 45 edges. Positive edges are blue and negative edges are red. Thicker lines represent stronger associations and thinner lines represent weaker associations. Nodes are coloured and organized according to groups A, B and C, which make up three subnetworks. In network 1 most edges are positive, with only few, very weak negative edges. The nodes with highest **strength** centrality are 3 and 9. The nodes with highest **betweenness** centrality are 5 and 9. The nodes with highest **clustering coefficients** are 6 and 4, which also have the lowest strength centrality. In network 2 the majority of edges are still positive, but there are more and stronger negative edges. **Path lengths** are shorter and **clustering coefficients** are larger than in network 1, resulting in a more integrated and denser network. In other words, there is reduced separation between nodes and reduced division between subnetworks A, B and C in network 2, compared to network 1. In network 2 the nodes with highest **strength** and **betweenness** centrality are 3 and 5. The nodes with highest **clustering coefficients** are 6 and 2, and 6 also has the lowest strength centrality. Overall, both networks are organized according to three subnetworks A, B and C, but increased integration and density in network 2 results in less clearly defined subnetworks.

Clustering coefficients are the number of associations among neighbours of a focal node over the maximum number of possible associations. A node may be central, but also redundant if its neighbours are also highly associated with one another i.e. if the node has a high clustering coefficient (Costantini et al., 2015). Average clustering coefficient is an index of density of the network. The 'clustcoef_auto' function was used to compute clustering coefficients.

Network structure of cognition in childhood

In order to examine the network structure of cognition in childhood (age 8) information, similarities, vocabulary, comprehension, arithmetic, digit span, picture completion, picture arrangement, block design, object assembly and digit symbol subtests of the WISC-III, as well as the sky search subtest from the TEA-Ch were analysed as nodes. Nodes were categorized by four subscales: 1) verbal (information, similarities, vocabulary, comprehension), 2) working memory (arithmetic, digit span), 3) perceptual (picture completion, picture arrangement, block design, object assembly and 4) processing speed (digit symbol coding, sky search) based on factor analytic studies of WISC-III structure (Wechsler, 1991). Group differences in edge weights, shortest paths and clustering coefficients were examined using regression in STATA software (version 14; Stata-Corp).

Sensitivity analysis I

In order to examine whether group differences in network structure could be due to differences in cognitive ability we matched individuals from the control, depression and psychotic experiences groups to the non-affective psychosis group on mean full-scale IQ at age 8. Differences in edge weights, clustering coefficients and shortest path

lengths between IQ-matched and unmatched networks were examined using regression in STATA software (version 14; Stata-Corp).

Change in network structure between childhood and adulthood

In order to examine the change in network structure between childhood (age 8) and early adulthood (age 20) identical versions of vocabulary, digit span, block design, digit symbol and sky search subtests administered at both ages were analysed as nodes. Main effects of group and age, as well as group-by-age interactions on edge weights, path lengths and clustering coefficients were examined using the ***mixed*** command for multilevel regression in STATA software (version 14; Stata-Corp).

Sensitivity analysis II

In order to adjust for any potential effects of medication on changes in network structure between childhood and adulthood, participants who were prescribed medication for psychotic experiences at age 18 were excluded in sensitivity analyses.

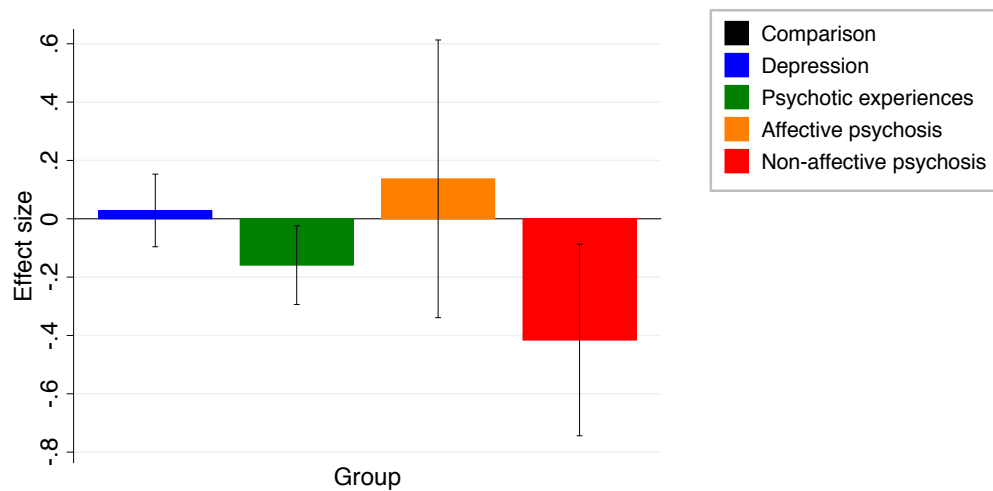
Results

Network structure of cognition in childhood

Demographic characteristics of individuals with available age 8 cognitive data and age 18 diagnostic interviews can be seen in **Table 3.3**. In the previous chapter we reported widespread group differences in cognitive functioning. **Figure 4.2** shows effect sizes (Cohen *d*) of full-scale IQ for depression, psychotic experiences, affective and non-affective groups at age 8. The depression and affective psychosis groups did not show significant differences compared to controls on full-scale IQ (Cohen $d=0.03$, $p=0.7$;

Cohen $d=0.14$, $p=0.6$). The psychotic experiences and non-affective psychosis groups showed small decrements on full-scale IQ (Cohen $d=-0.16$, $p=0.02$; Cohen $d=-0.42$, $p=0.01$).

Figure 4.2 Effect sizes for depression, psychotic experiences, affective and non-affective psychosis groups on full-scale IQ at age 8



Network visualization of associations between cognitive subtests in control, depression, psychotic experiences, affective psychosis and non-affective psychosis groups can be seen in **Figures 4.3 and 4.4** (node placement in **Figure 4.4** is based on controls to facilitate comparison). Inspection of **Figure 4.3** suggests that the size of networks did not differ between groups, except in the affective psychosis group, which showed a more concentrated network. Group differences were seen in network organization, however. Clear organization of subnetworks according to the four domains (verbal, working memory, perceptual and processing speed) can be seen in the control group network. Small deviations from controls can be seen in the depression and psychotic experiences groups, in the form of increased distance between picture arrangement and

other perceptual tests in the depression group and decreased distance between verbal and working memory subscales in the psychotic experiences group. The network structure of affective and non-affective psychosis groups showed large deviations from controls. The affective group showed a dense network overall, with vocabulary and sky search nodes in relative isolation. The perceptual subnetwork appeared relatively intact, unlike verbal and working memory subnetworks. In the non-affective psychosis group only the processing speed subnetwork remained intact with disorganization seen across the network.

Figure 4.3 Network visualization of associations between cognitive subtests by group*

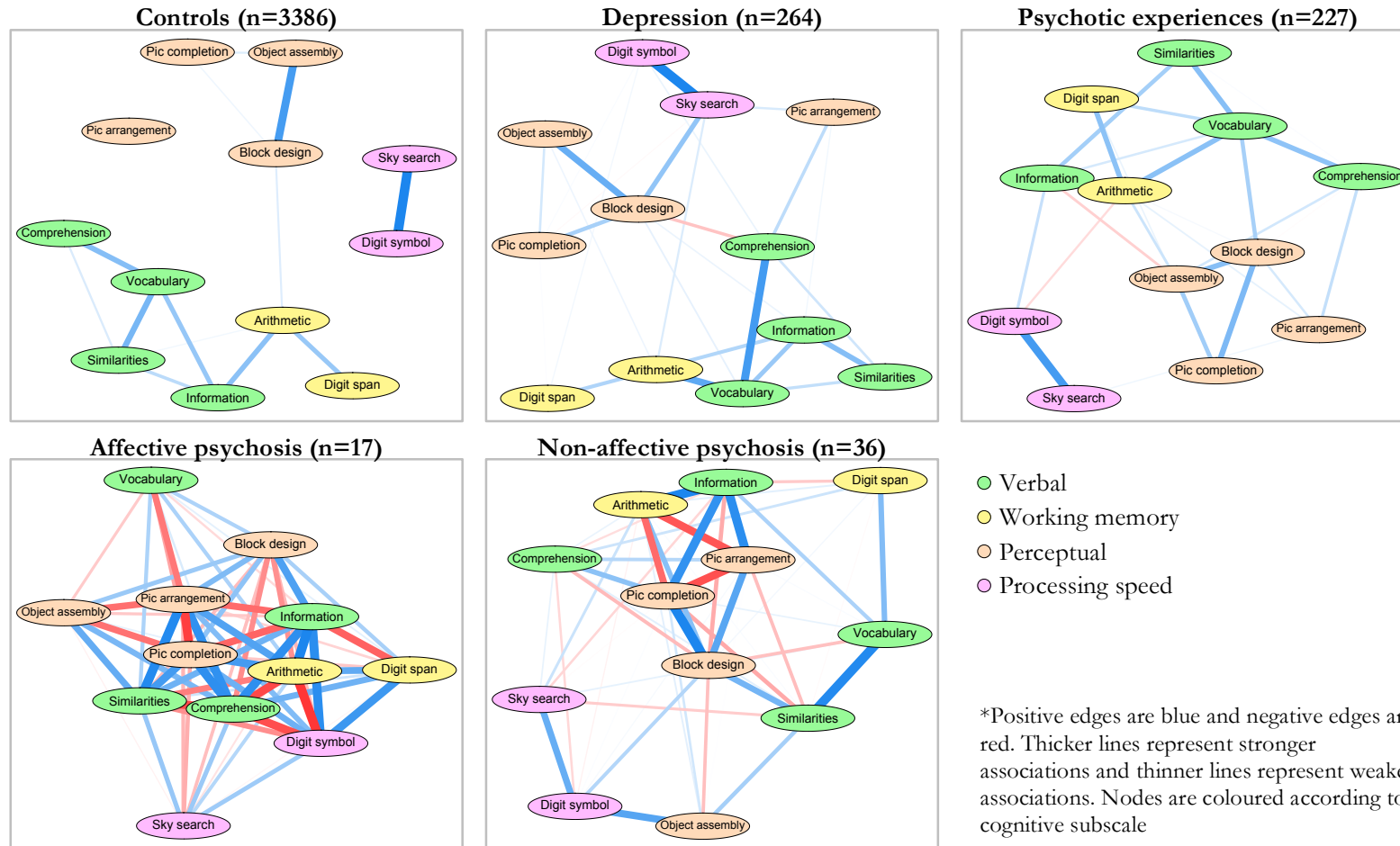
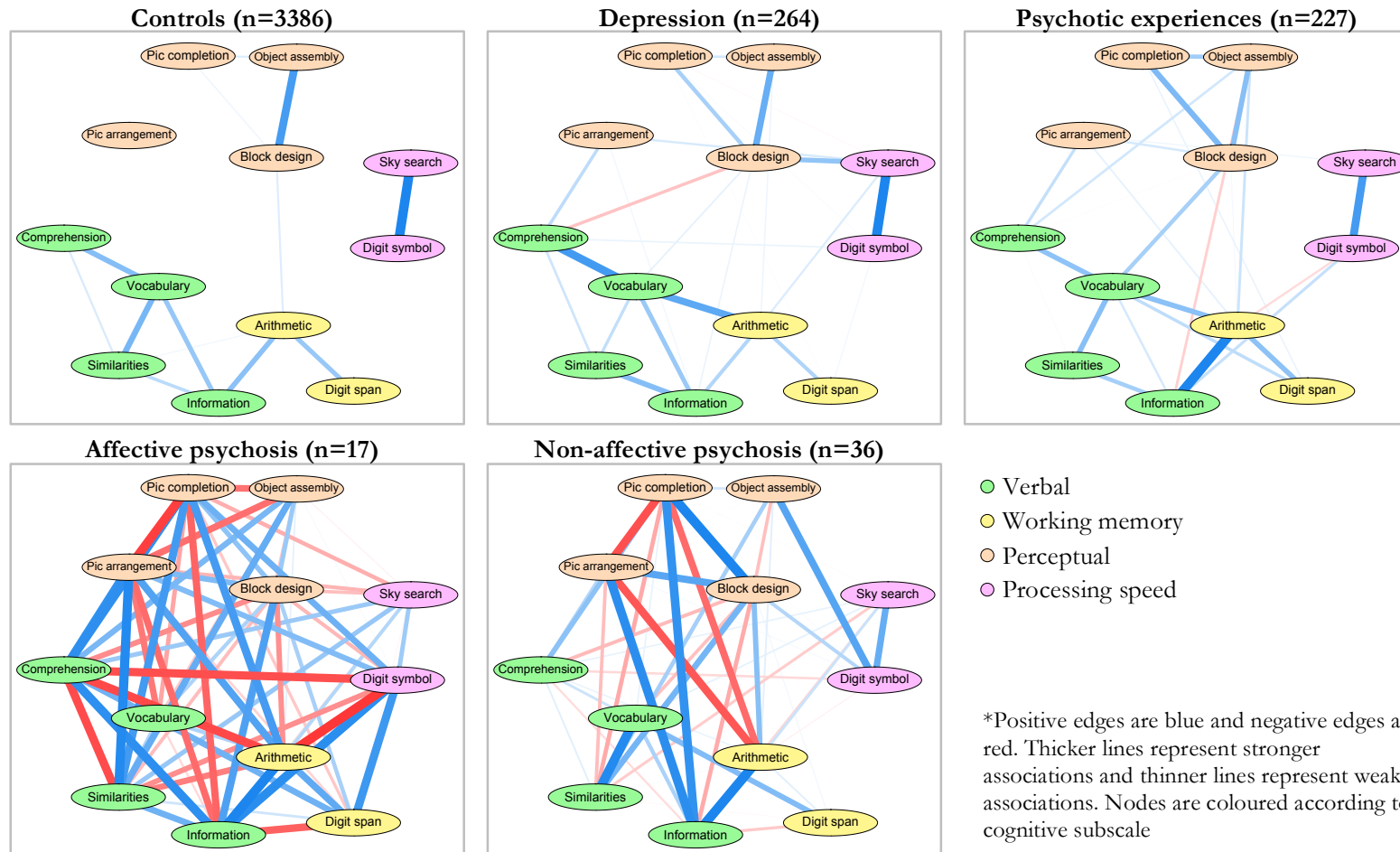


Figure 4.4 Network visualization of associations between cognitive subtests by group (node placement based on controls)*



Distributions of edge weights (partial correlations) and path lengths for each group can be seen in **Figure 4.5**. Control, depression and psychotic experiences groups showed a majority of small, positive edge weights. Significantly larger positive and negative edge weights were seen in the affective ($\beta=0.44, p<.001, \beta=-0.47, p<.001$) and non-affective ($\beta=0.16, p<.001, \beta=-0.19, p=.002$) psychosis groups compared to controls, suggesting greater connectivity, but also dysconnectivity, between cognitive processes in these groups. Non-affective psychosis, affective psychosis, psychotic experiences and depression groups showed significantly shorter path lengths compared to controls ($\beta=-10.2, p<.001, \beta=-12.7, p<.001, \beta=-5.9, p<.001, \beta=-5.5, p<.001$), suggesting greater network integration in all groups.

Strength and betweenness centrality measures were each plotted against clustering coefficients for the control, depression, psychotic experiences, affective and non-affective psychosis groups (**Figure 4.6**). Horizontal lines represent average (strength or betweenness) centrality and vertical lines represent average clustering coefficient. In the control, depression and psychotic experiences groups three central nodes without high clustering emerged: vocabulary, block design and arithmetic. In the affective and non-affective psychosis groups two central nodes without high clustering emerged: comprehension and picture arrangement, and similarities and block design, respectively.

Overall, the most central nodes in the control, depression and psychotic experiences groups fell under three subscales: verbal, perceptual and working memory, suggesting separable cognitive hubs already present in childhood (age 8) in these groups. The affective and non-affective psychosis groups, on the other hand, showed evidence for perceptual and verbal, but not working memory hubs. Psychotic experiences, affective

and non-affective psychosis groups showed larger clustering coefficients than controls ($\beta=0.02, p=.04, \beta=0.49, p<.001, \beta=0.17, p<.001$), suggesting greater network density in these groups.

Figure 4.5 Histograms of edge weights (partial correlations) and path lengths between nodes by group

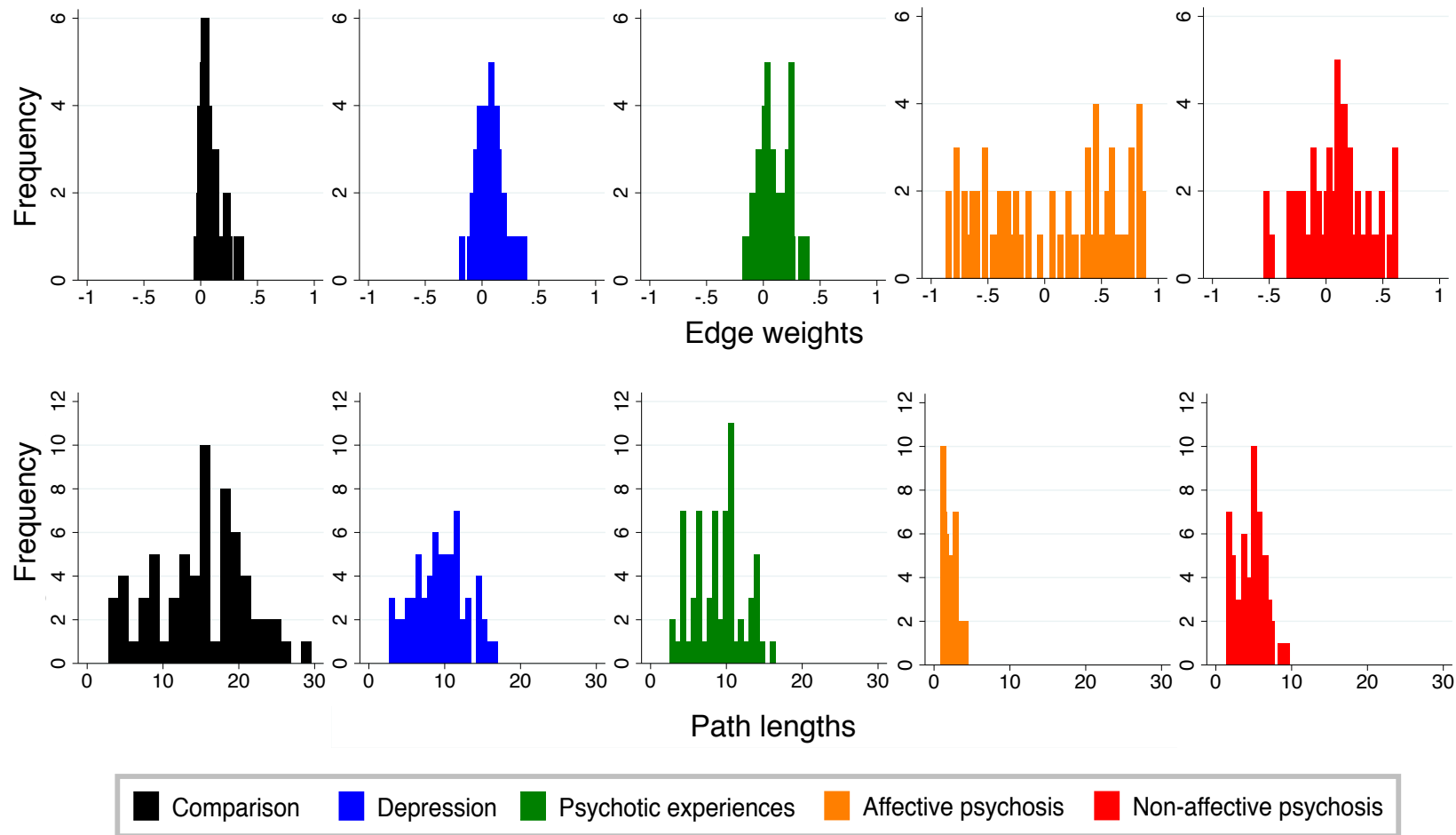
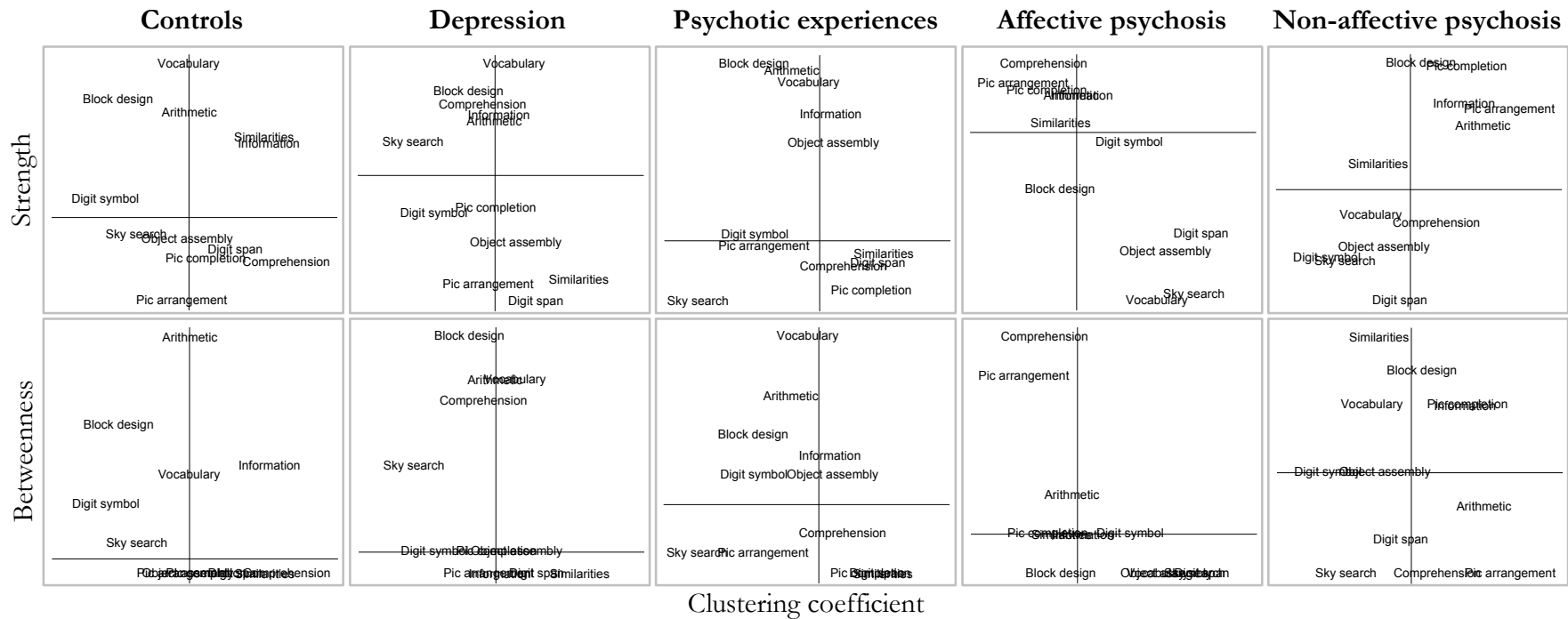


Figure 4.6 Strength and betweenness node centrality plotted against clustering coefficients for each group*



*Horizontal lines represent average (strength or betweenness) centrality and vertical lines represent average clustering coefficient.

Sensitivity analysis I - adjusting for IQ

Network visualization of associations between cognitive subtests in IQ-matched control, depression, and psychotic experiences groups can be seen in **Figure 4.7** (node placement in the bottom row is based on unmatched controls for ease of comparison). Matching groups to the non-affective psychosis group on IQ did not lead to substantial changes in network size and organization. Organization according to domains (verbal, working memory, perceptual and processing speed) can be seen in all group networks, although picture arrangement showed increased distance from other perceptual nodes in controls.

Distributions of edge weights (partial correlations) and path lengths for each group can be seen in **Figure 4.8**. All groups showed a majority of small, positive edge weights. No group showed statistically significant differences in edge weights (positive and negative) or path lengths between IQ-matched and unmatched networks. Together with **Figure 4.7**, inspection of **Figure 4.8** suggests interconnected and organized cognitive networks in control, depression and psychotic experiences groups when matched on IQ to the non-affective psychosis group.

Strength and betweenness centrality were each plotted against clustering coefficients for IQ-matched control, depression and psychotic experiences groups (**Figure 4.9**).

Horizontal lines represent mean (strength or betweenness) centrality and vertical lines represent mean clustering coefficient. The most central nodes without high clustering in the control and psychotic experiences group were still vocabulary, block design and arithmetic. In the depression group, picture completion and information showed high centrality without higher clustering and arithmetic remained a central node to the

network. Overall, the most central nodes in the control, depression and psychotic experiences groups still fell under three domains: verbal, perceptual and working memory. The IQ-matched depression network showed higher clustering coefficients than the unmatched network ($\beta=0.01, p=.030$). No statistically significant differences in average clustering coefficients were seen between IQ-matched and unmatched control and psychotic experiences groups.

Figure 4.7 Sensitivity analysis I - Network visualization of associations between cognitive subtests for control, depression and psychotic experiences groups matched on IQ to the non-affective psychosis group*

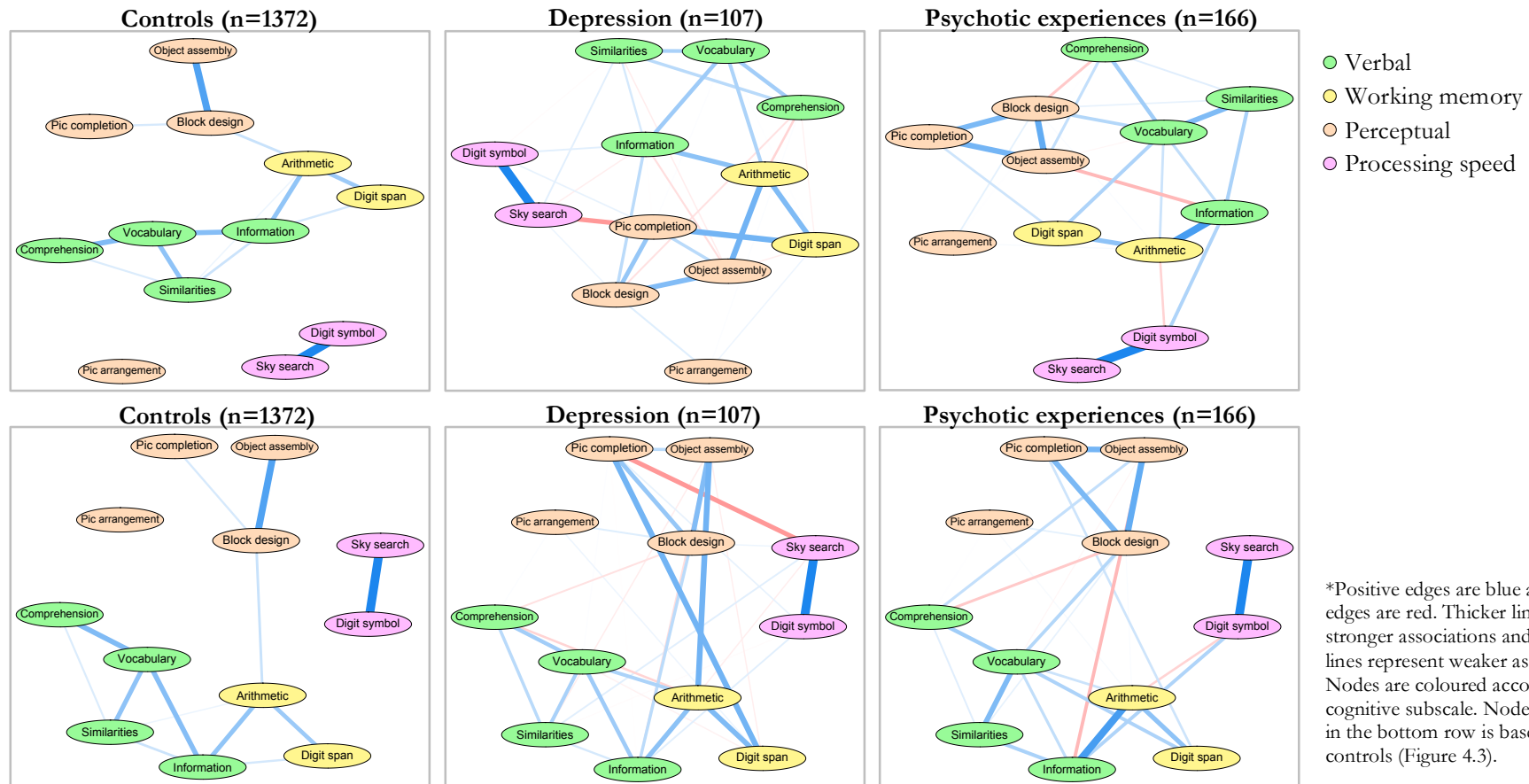


Figure 4.8 Sensitivity analysis I - Histograms of edge weights for control, depression and psychotic experiences groups matched on IQ to the non-affective psychosis group

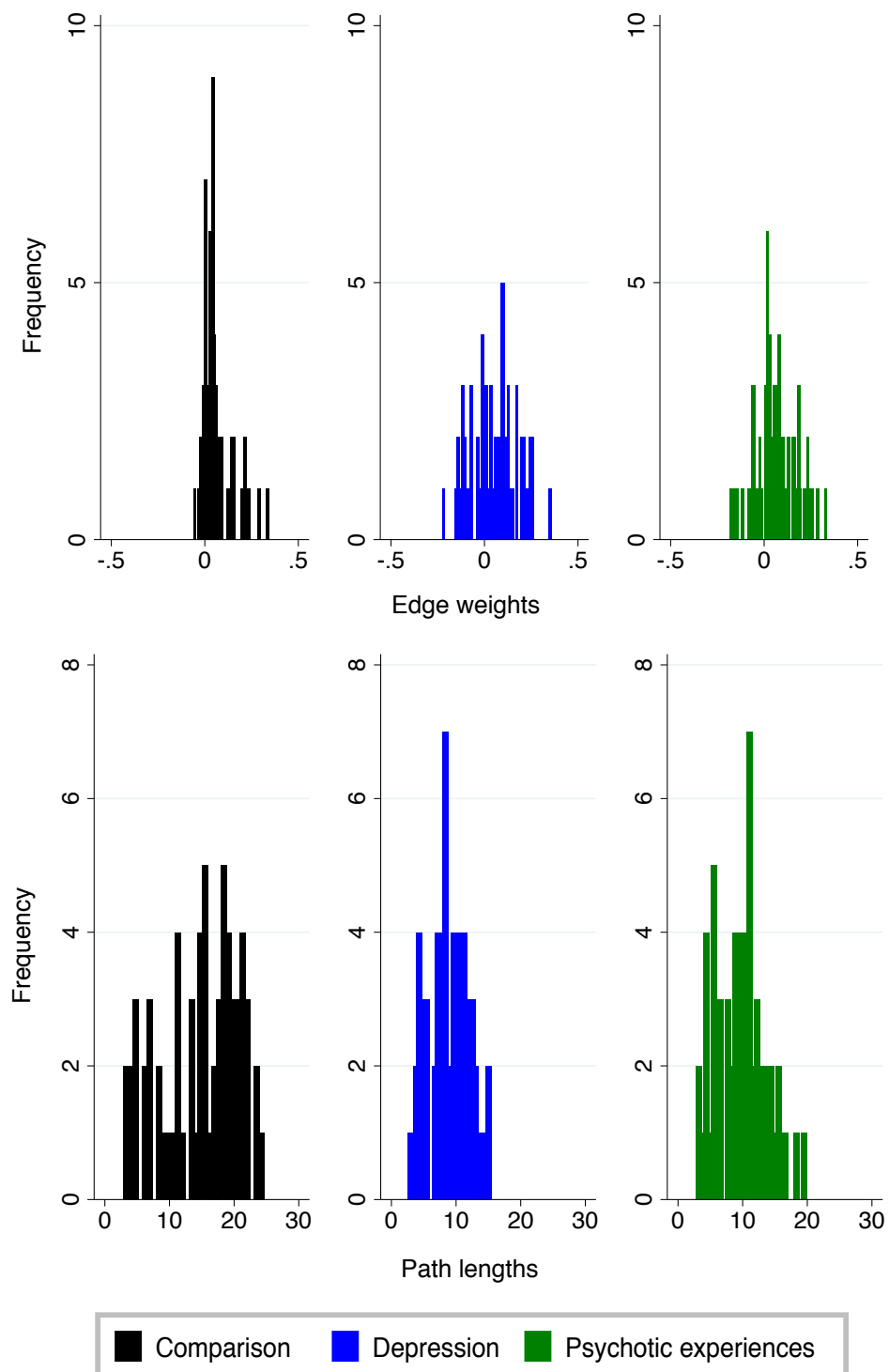
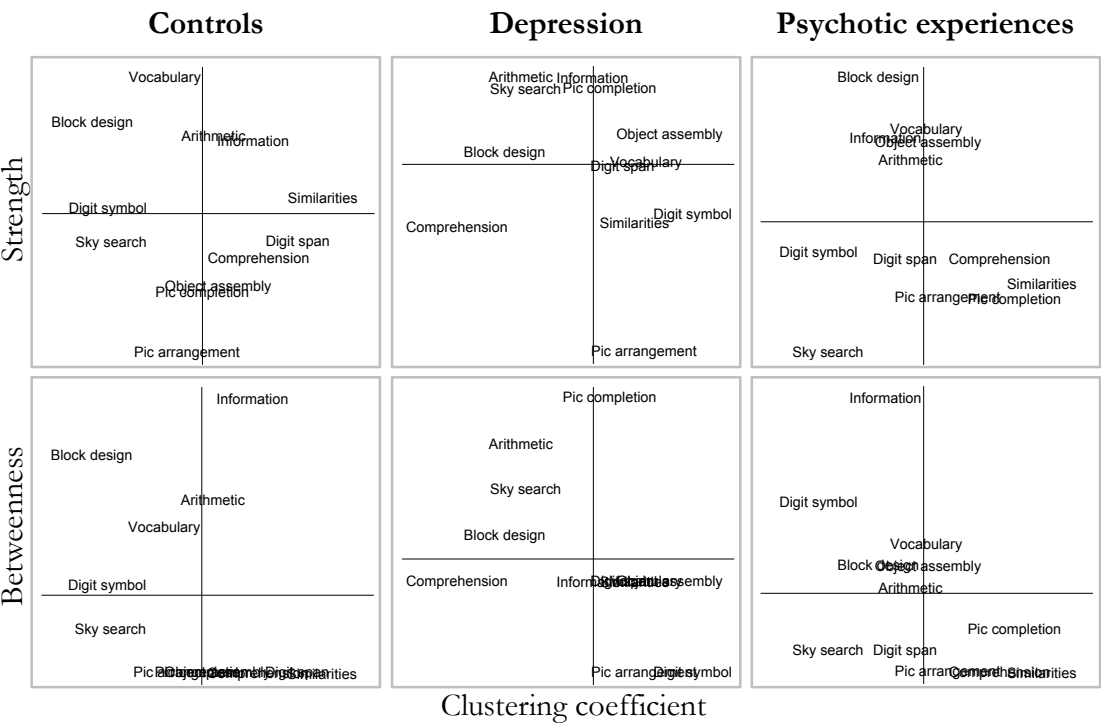


Figure 4.9 Sensitivity analysis I - Strength and betweenness centrality plotted against clustering coefficients for control, depression and psychotic experiences groups matched on IQ to the non-affective psychosis group*



*Horizontal lines represent average (strength or betweenness) centrality and vertical lines represent average clustering coefficient.

Change in network structure between childhood and adulthood

Demographic characteristics of the high-risk longitudinal sample can be seen in **Table 3.5**. Network visualization of associations between cognitive subtests in control, depression, psychotic experiences, affective psychosis and non-affective psychosis groups at ages 8 and 20 can be seen in **Figures 4.10 and 4.11** (node placement in **Figure 4.11** is based on controls at age 8 for ease of comparison). **Figure 4.12** shows positive and negative edge weights (partial correlations), path lengths and clustering coefficients at ages 8 and 20. **Figure 4.13** shows strength and betweenness node centrality each plotted against clustering coefficients at both ages. Inspection of **Figures 4.10-13** suggests small changes in the cognitive network of controls between childhood (age 8) and adulthood (age 20). Vocabulary was less integrated at age 20 than at age 8 (**Figure 4.10**). Edge weights were small and mostly positive at both ages (**Figures 4.11-12**). Path lengths and clustering coefficients also remained relatively stable between ages 8 and 20 (**Figure 4.12**). Finally, there was a shift from sky search to digit span as the most central node without high clustering over time (**Figure 4.13**). Overall, connectivity (edge weights), integration (path lengths) and density (clustering coefficients) showed little change between childhood and adulthood in the control group. There was, however, increased reliance on working memory (digit span) functions with increasing age.

Depression, psychotic experiences, affective and non-affective psychosis groups showed greater change in cognitive network structure between childhood and adulthood. Group differences in edge weights did not reach statistical significance, but inspection of **Figures 4.10-4.12** suggests an increase in negative edge weights in the

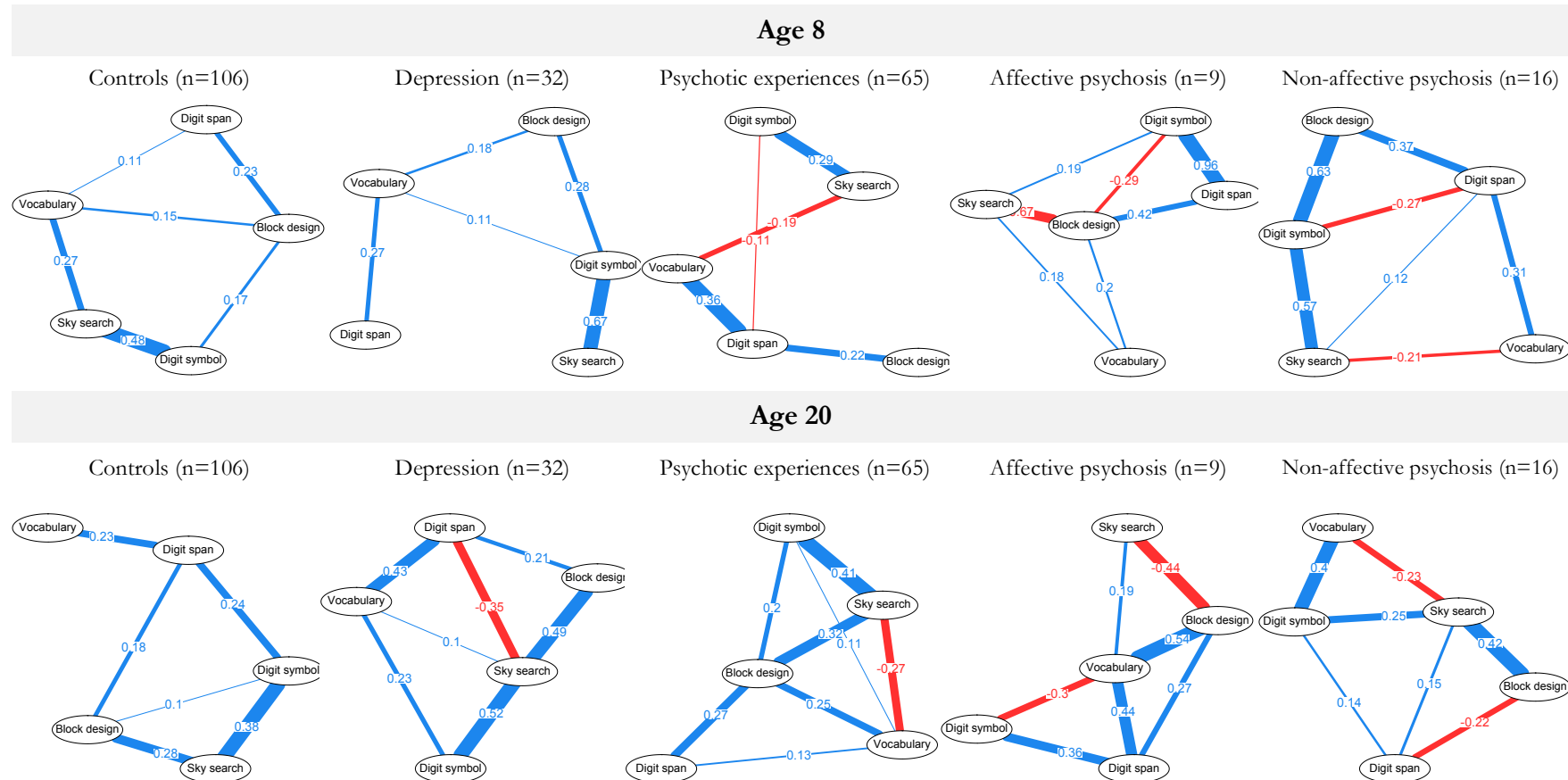
depression and psychotic experiences groups over time, and larger positive and negative edge weights in the affective and non-affective psychosis groups at both ages. Significant main effects on path length for affective ($\beta=-2.37, p=.04$) and non-affective psychosis groups ($\beta=-2.77, p=.01$) suggested shorter overall path lengths and greater integration over ages 8 and 20 in these groups. A significant group-by-age interaction on path length for the depression group ($\beta=-3.15, p=.04$) suggested decreasing path length and increasing integration between ages 8 and 20 in this group.

Like controls, depression, psychotic experiences, affective and non-affective psychosis groups showed a change in the most central node without high clustering between ages 8 and 20. The depression and non-affective psychosis groups showed a shift from digit symbol to sky search. The psychotic experiences group showed a shift from digit span to block design. In the affective psychosis group block design was central at both ages, with vocabulary also becoming more central at age 20. Significant main effects on clustering coefficient for affective ($\beta=0.16, p<.001$) and non-affective ($\beta=0.10, p=.001$) psychosis groups suggested higher overall clustering and therefore, greater network density over ages 8 and 20 in these groups (**Figure 4.12**). A significant group-by-age interaction on clustering coefficients in the psychotic experiences group ($\beta=0.09, p=.04$) suggested increasing clustering and therefore, increasing network density between ages 8 and 20 in this group (**Figure 4.12**).

Overall, affective and non-affective psychosis groups showed greater connectivity and dysconnectivity (larger positive and negative edge weights), integration (shorter path lengths) and density (larger clustering coefficients) than controls at both ages 8 and 20. The psychotic experiences group showed increasing density (increasing clustering

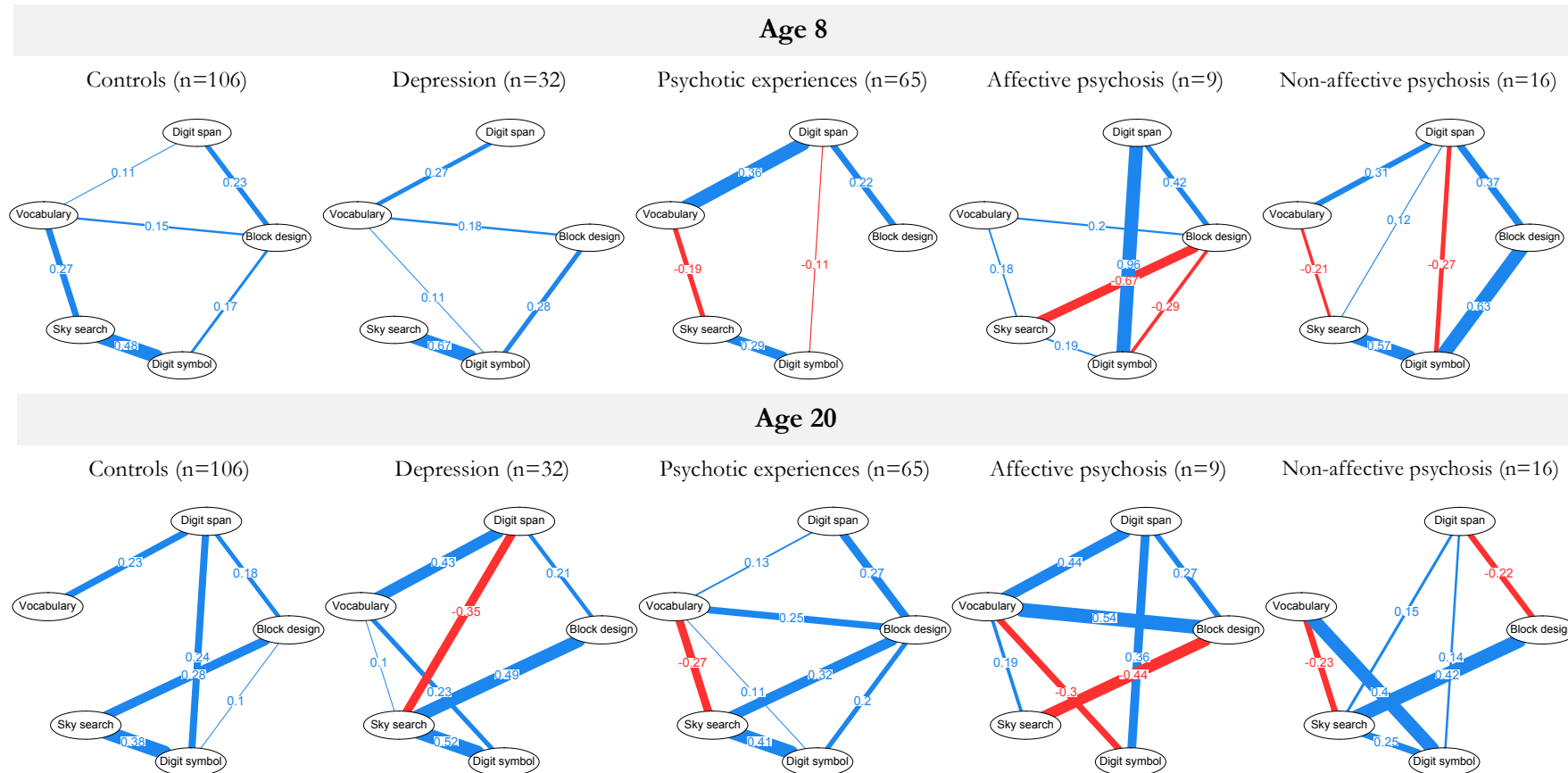
coefficients), and the depression group showed increasing integration (decreasing path lengths) between childhood and adulthood.

Figure 4.10 Network visualization of associations between cognitive subtests at ages 8 and 20*



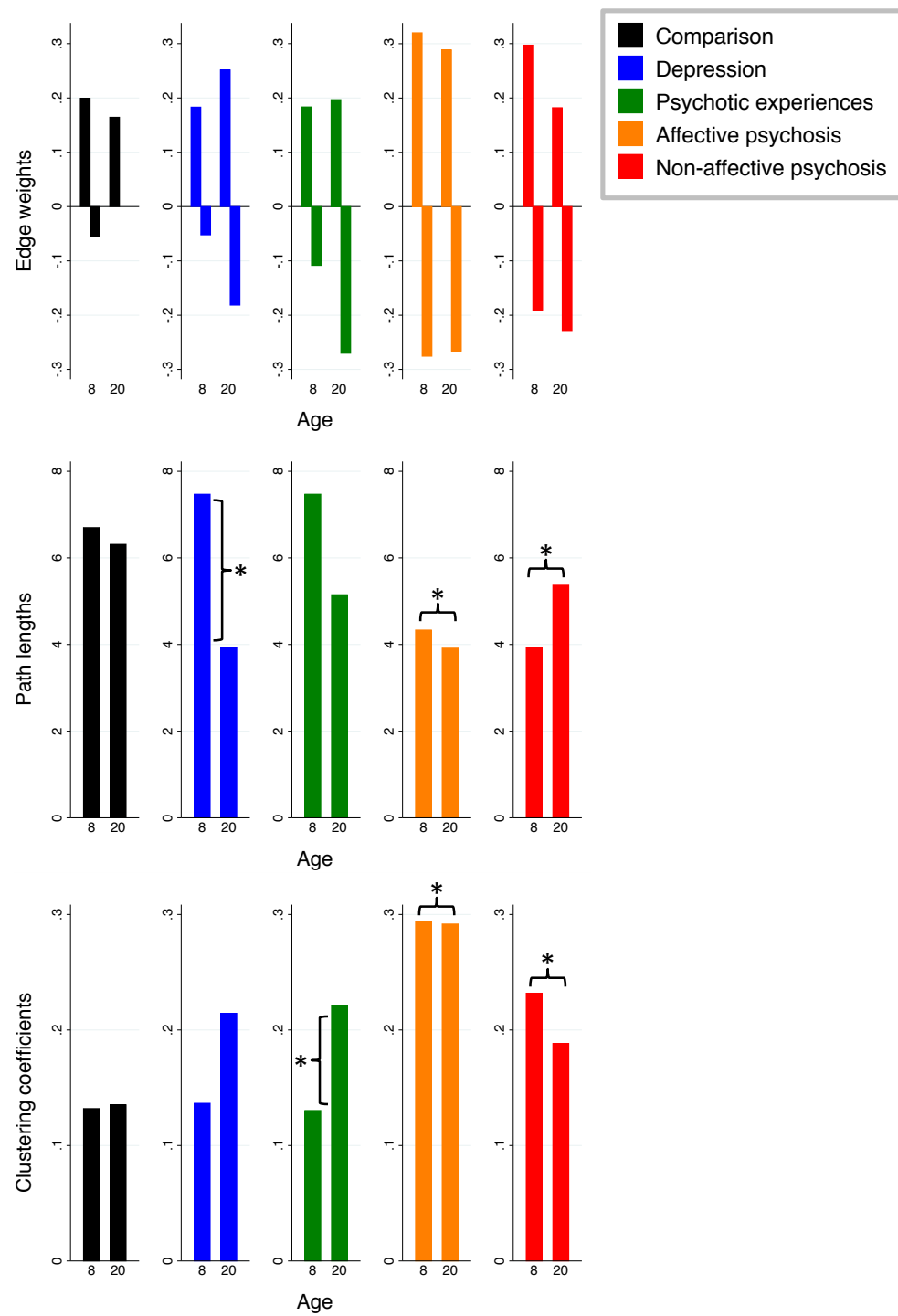
*Positive edges are blue and negative edges are red. Thicker lines represent stronger associations and thinner lines represent weaker associations.

Figure 4.11 Network visualization of associations between cognitive subtests by groups at ages 8 and 20 (node placement based on controls at age 8)*



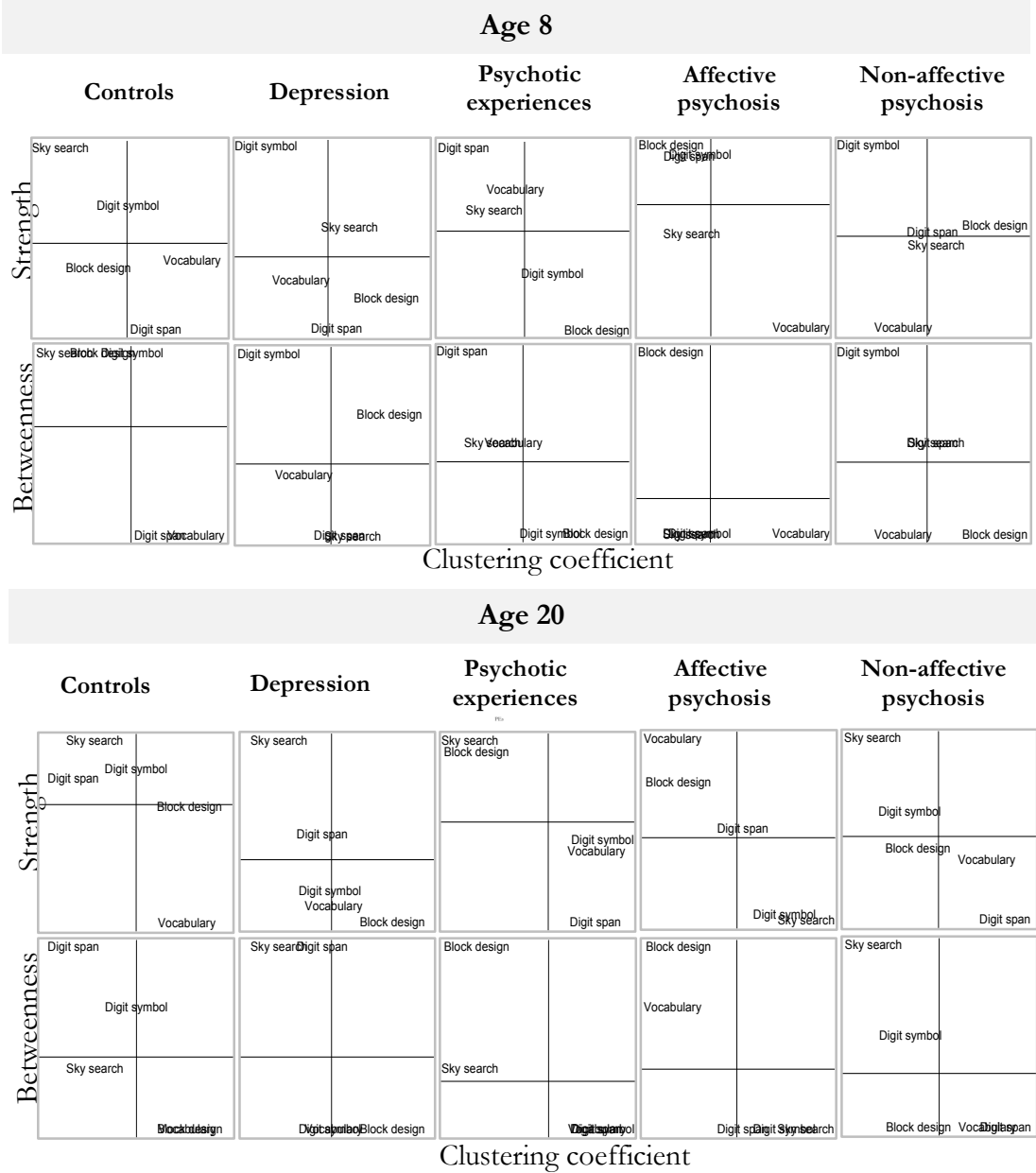
*Positive edges are blue and negative edges are red. Thicker lines represent stronger associations and thinner lines represent weaker associations.

Figure 4.12 Edge weights, path lengths and clustering coefficients at ages 8 and 20*



* $p < .05$

Figure 4.13 Node centrality measures by clustering coefficients at ages 8 and 20

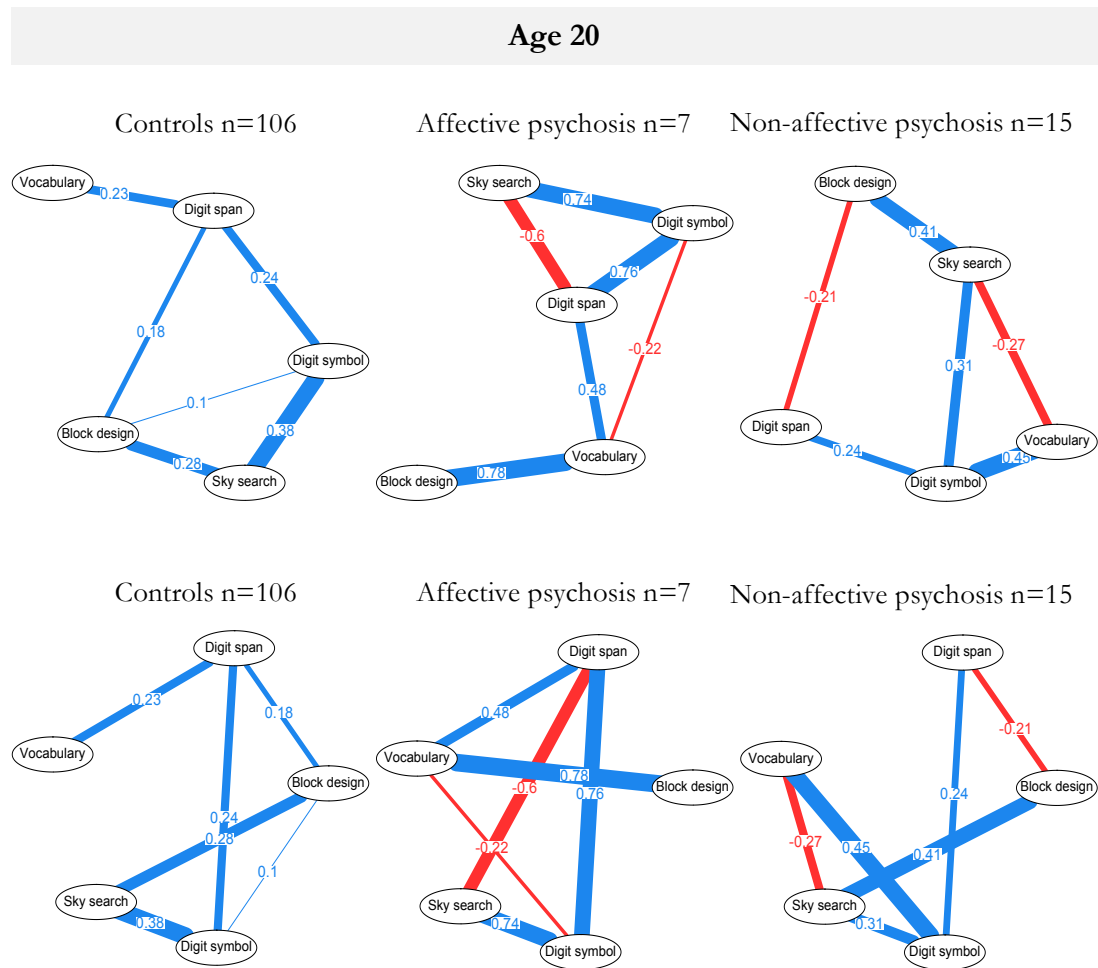


*Horizontal lines represent average (strength or betweenness) centrality and vertical lines represent average clustering coefficient.

Sensitivity analysis II - adjusting for medication

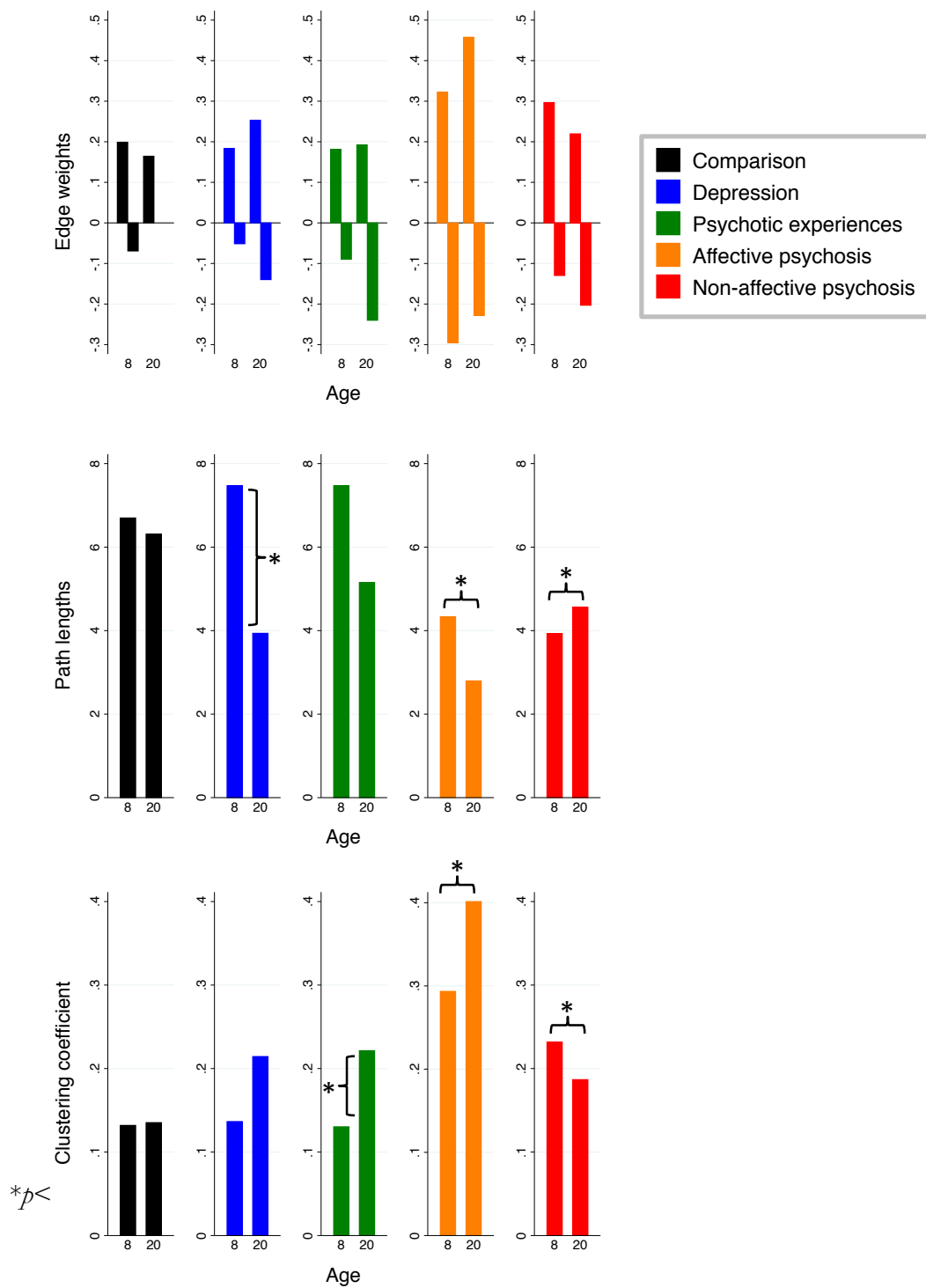
At age 18, two participants from the affective psychosis group and one participant from the non-affective psychosis group reported being prescribed medication. These three participants were excluded from sensitivity analyses. Network visualizations for control, affective and non-affective groups can be seen in **Figure 4.14** (node placement in the bottom row is based on controls at age 8 for ease of comparison). Positive and negative edge weights (partial correlations), path lengths and clustering coefficients at ages 8 and 20 by group can be seen in **Figure 4.15**. No statistically significant main effects of age or group, or group-by-age interactions were seen in edge weights. Main effects on path lengths for affective ($\beta=-2.37, p=.03$) and non-affective psychosis groups ($\beta=-2.77, p=.01$) remained statistically significant, suggesting greater network integration across ages 8 and 20 in these groups. Significant main effects on clustering coefficients for affective ($\beta=0.16, p<.001$) and non-affective ($\beta=0.10, p=.001$) psychosis groups suggested higher network density across ages 8 and 20 in these groups (**Figure 4.15**). Overall, excluding participants who had been prescribed medication did not substantially alter the results.

Figure 4.14 Sensitivity analysis II - Network visualization of associations between cognitive subtests at age 20 for control, affective and non-affective psychosis groups*



*Positive edges are blue and negative edges are red. Thicker lines represent stronger associations and thinner lines represent weaker associations. Node placement in the second row is based on controls at age 8 (**Figure 4.10**).

Figure 4.15 Sensitivity analysis II - Edge weights, path lengths and clustering coefficients at ages 8 and 20



Discussion

This study provides evidence of aberrant connectivity and organization in the network structure of cognitive processes in individuals with psychotic disorders. Our findings are in line with imaging studies of brain connectivity (Fornito et al., 2012) and factor analytic studies of cognitive functioning in schizophrenia (Nuechterlein et al., 2004).

Our findings are novel in several ways. First, we found group differences in cognitive network structure in childhood (age 8) even in the absence of differences in performance. An extensive literature documents large cognitive deficits in schizophrenia (Reichenberg and Harvey, 2007) and milder deficits have been reported in depression, psychotic experiences and affective psychotic disorders (Millan et al., 2012; Zanelli et al., 2010; Mollon et al., 2015). In our sample, only individuals with psychotic experiences and non-affective psychosis showed small IQ deficits at age 8. However, anomalies in cognitive network structure were seen across groups, albeit to different extents. Cognitive networks in control, psychotic experiences and depression groups were organized by domain and central nodes each belonged to these domains, suggesting separable, yet equally important, cognitive subnetworks and hubs. Affective and non-affective psychosis groups showed little evidence of subnetworks or hubs, suggesting a gross restructuring of cognitive functions in individuals with psychotic disorder. Our finding of disruption to central/hub cognitive processes lends support to the hubopathy hypothesis (Rubinov and Bullmore, 2013), which postulates that schizophrenia is characterized by abnormalities in brain hubs.

Affective and non-affective psychosis groups also showed greater network connectivity, dysconnectivity (stronger positive and negative associations), density (greater clustering) and integration (shorter path lengths) than controls. Greater network integration was also seen in depression and psychotic experiences groups, with the latter also showing greater density. Previous factor analytic studies have shown stronger associations between cognitive processes in schizophrenia (Dickinson et al., 2006; Haring et al., 2015; Strauss and Summerfelt, 2003). Imaging studies have reported increased clustering within brain regions (van den Heuvel et al., 2010; Bassett et al., 2008) and decreased path length (Rubinov et al., 2009) in schizophrenia patients. Increased integration and density may be compensatory or directly pathological (Bullmore and Bassett, 2011) since an ideal network structure has been suggested to depend on optimal trade-off between the two (Tononi et al., 1994). Our findings suggest that alterations in network connectivity, density and integration may extend, albeit to different extents, to affective and subclinical psychosis (Drakesmith et al., 2015), as well as depression. Moreover, considering only cognitive performance may obscure important etiological clues since anomalies in cognitive networks were seen even in the absence of decrements in performance.

Second, we were able to investigate changes in cognitive network structure between childhood (age 8) and adulthood (age 20) in a longitudinal high-risk subsample. Controls did not show substantial changes in network structure between childhood and adulthood, bar an increase in reliance on working memory functions. This finding is in line with evidence that prefrontal areas implicated in executive functions mature relatively late (Casey et al., 2005). Depression, psychotic experiences, affective and non-affective psychosis groups, on the other hand, showed greater reliance on attention and

visuospatial processes, perhaps reflecting delayed cognitive development. Increased reliance in schizophrenia patients on low-level cognition, rather than executive functions, has been reported during digit symbol coding (Knowles et al., 2015). Our findings suggest that the development of higher cognitive functions may be delayed or even absent in young people with psychotic disorders, but also subclinical psychotic experiences and depression, who consequently rely on low-level cognitive processes.

Increasing network integration (decreasing path lengths) and density (increasing clustering coefficients) between childhood and adulthood were seen in depression and psychotic experiences groups, respectively. Affective and non-affective groups, on the other hand, showed early and relatively stable deviations in network integration and density. Early abnormalities in cognitive network structure lend support to neurodevelopmental models of schizophrenia, which hypothesize that early environmental insults and/or genetic risk factors lead to subtle neurobehavioral anomalies already detectable in childhood, many years before illness onset (Murray and Lewis, 1987; Weinberger, 1987). Interestingly, however, small decreases in integration (increasing path lengths) and density (decreasing clustering) between childhood (age 8) and adulthood (age 20) were seen in the non-affective psychosis group, although this did not reach statistical significance. These findings require replication, but may begin to explain how quantitatively similar cognitive network anomalies in affective and non-affective psychosis groups result in very different cognitive profiles.

Third, we were able to provide twofold evidence that cognitive network abnormalities are not simply due to lower cognitive ability. Firstly, only individuals with psychotic experiences and non-affective psychotic disorder showed small IQ deficits at age 8, yet

anomalies in cognitive network structure were also seen in the depression and affective psychosis groups who showed above average IQ scores. Indeed, abnormalities in connectivity, integration and density were similar in the affective and non-affective psychosis groups despite their distinct profiles of cognitive performance. Secondly, we adjusted for cognitive ability at age 8 by matching control, depression and psychotic experiences groups to the non-affective psychosis group on IQ. None of the IQ-matched groups showed statistically significant differences in cognitive network structure compared to their respective unmatched groups, suggesting again that aberrations in cognitive network structure seen in individuals with non-affective psychosis were not simply due to lower cognitive ability in this group.

Our findings have important theoretical and clinical implications. First, we did not find strong evidence for either differentiation or dedifferentiation. Instead, our findings suggest early, complex alterations in cognitive network structure in psychotic disorders, with increased connectivity, but also dysconnectivity, between functions, as well as increased network integration and density. Early environmental exposures or genetic risk factors may cause diffuse disruption in brain connectivity, leading, in turn, to disruptions in cognitive processes and poor cognitive control (Lesh et al., 2011).

Clinically, our findings suggest the importance of looking beyond cognitive performance as a risk/resilience factor since aberrant connectivity was found in the absence of cognitive deficits. Subtle deviations in recruitment of different cognitive functions may be helpful in the prediction of future psychopathology and could prove to be valuable targets in cognitive remediation efforts.

This study has certain limitations. First, while we were able to adjust for prescribed medications in our analyses, we were not able to adjust for illicit drug or alcohol use, both of which may have adverse effects on cognition (Macleod et al., 2004; Squeglia et al., 2009). However, it is extremely unlikely that illicit drug or alcohol use could account for the differences in cognitive network structure seen in childhood (age 8), when substantial deviations in cognitive network structure were already present. Second, only five cognitive subtests were available for longitudinal analyses. However, the comprehensive results at age 8 corroborate those from the longitudinal analyses. Future longitudinal studies, including comprehensive cognitive batteries and brain imaging, are needed to investigate the network structure of cognitive and brain function associated with psychosis and other psychiatric disorders. Such studies could help elucidate cognitive and physiological pathways to disease and suggest targets for intervention.

Conclusions

We found aberrant connectivity and disorganization of cognitive networks in individuals with psychotic disorder. Subtle deviations in network density and integration were also seen in individuals with psychotic experiences and depression. Deviations in cognitive network structure were seen even in the absence of cognitive deficits, suggesting the importance of considering, not only performance, but also the manner in which performance is attained in early detection and intervention efforts.

Summary and Discussion

Summary of findings

First, I examined the association between subclinical psychotic experiences and cognitive functioning in a general population adult sample and found evidence for mild cognitive deficits in adults with psychotic experiences. Specifically, adults with psychotic experiences showed significant impairments in verbal and memory functions, but not processing speed. The cognitive profile of adults with subclinical psychotic experiences differed, therefore, from that of patients with clinical psychosis. Moreover, only older adults with psychotic experiences showed medium to large working memory and memory deficits when adjusting for sociodemographic factors, psychiatric morbidity and cannabis use. First-degree relatives also had a significant verbal, but not memory impairment.

Second, I examined the course of cognitive functioning in individuals with non-affective psychotic disorder, affective psychotic disorder, psychotic experiences and depression through infancy (age 18 months), childhood (age 8) adolescence (age 15) and early adulthood (age 20). Individuals with non-affective psychotic disorder showed IQ decline beginning in infancy and peaking in early adulthood. Between childhood and adulthood, individuals with non-affective psychosis showed slowed growth in processing speed, working memory and attention, while deficits in language and visuospatial functions did not progress over time. Individuals with depression, psychotic experiences and affective psychotic disorder also showed a degree of cognitive impairment in certain functions, but only those with non-affective psychotic

disorder showed large, progressively increasing deficits across multiple cognitive domains.

Third, I examined the network structure of cognitive functioning in childhood (age 8), as well as changes in network structure between childhood (age 8) and adulthood (age 20) in individuals with non-affective psychotic disorder, affective psychotic disorder, psychotic experiences and depression. Non-affective psychotic disorder and affective psychotic disorder groups showed disorganization and dysconnectivity in cognitive networks in childhood (age 8). Subtle deviations in network density and integration were also seen at this age in individuals with psychotic experiences and depression. Affective psychosis and depression groups showed deviations in network structure despite showing above average cognitive performance. Moreover, matching control, depression and psychotic experiences groups on IQ to individuals with non-affective psychotic disorder, who showed a small IQ deficit, revealed a similar pattern of results as when groups were unmatched. Between childhood (age 8) and adulthood (age 20), controls showed increased reliance on working memory, while depression, psychotic experiences, affective and non-affective psychosis groups remained reliant on lower-level cognitive processes. Depression and psychotic experiences groups showed increasing network dysconnectivity, integration and density between childhood and adulthood, while affective and non-affective groups showed early, relatively stable deviations in network structure.

Integration of thesis findings

In the first study, only older adults with psychotic experiences showed medium to large cognitive deficits when adjusting for sociodemographic factors. While the age range (16 to 34 years) of young adults in this sample coincided with the age range of psychosis onset (Kessler et al., 2007), young individuals with psychotic experiences showed only small neuropsychological impairment and even above average scores in certain cognitive domains. Thus, the cognitive profile of young adults reporting psychotic experiences differed substantially, in this sample, from that of patients with clinical psychotic disorder. Moreover, the most severe cognitive impairment in schizophrenia has been reported to be in processing speed (Dickinson et al., 2007; Knowles et al., 2010), but there was only a weak association between psychotic experiences and processing speed. These findings are in line with the notion that higher cognitive ability in individuals with psychotic manifestations may confer resilience against transitioning to clinical psychosis (Green et al., 2004). Young people who report psychotic experiences and show, for example, substantial and increasing processing speed deficits may be most at risk of developing a clinical psychotic disorder.

In the second study, psychotic experiences ascertained in late adolescence (age 18) were associated with a small, stable, general cognitive deficit from infancy through to adulthood, in line with results from the first study. In addition, there were small lags in processing speed and attention between childhood and adulthood (**Figure 5.1** summarizes findings of studies, which used data from the Avon Longitudinal Study of Parents and Children (ALSPAC)). The younger age at which individuals reported psychotic experiences in this sample, compared to the sample used in the first study,

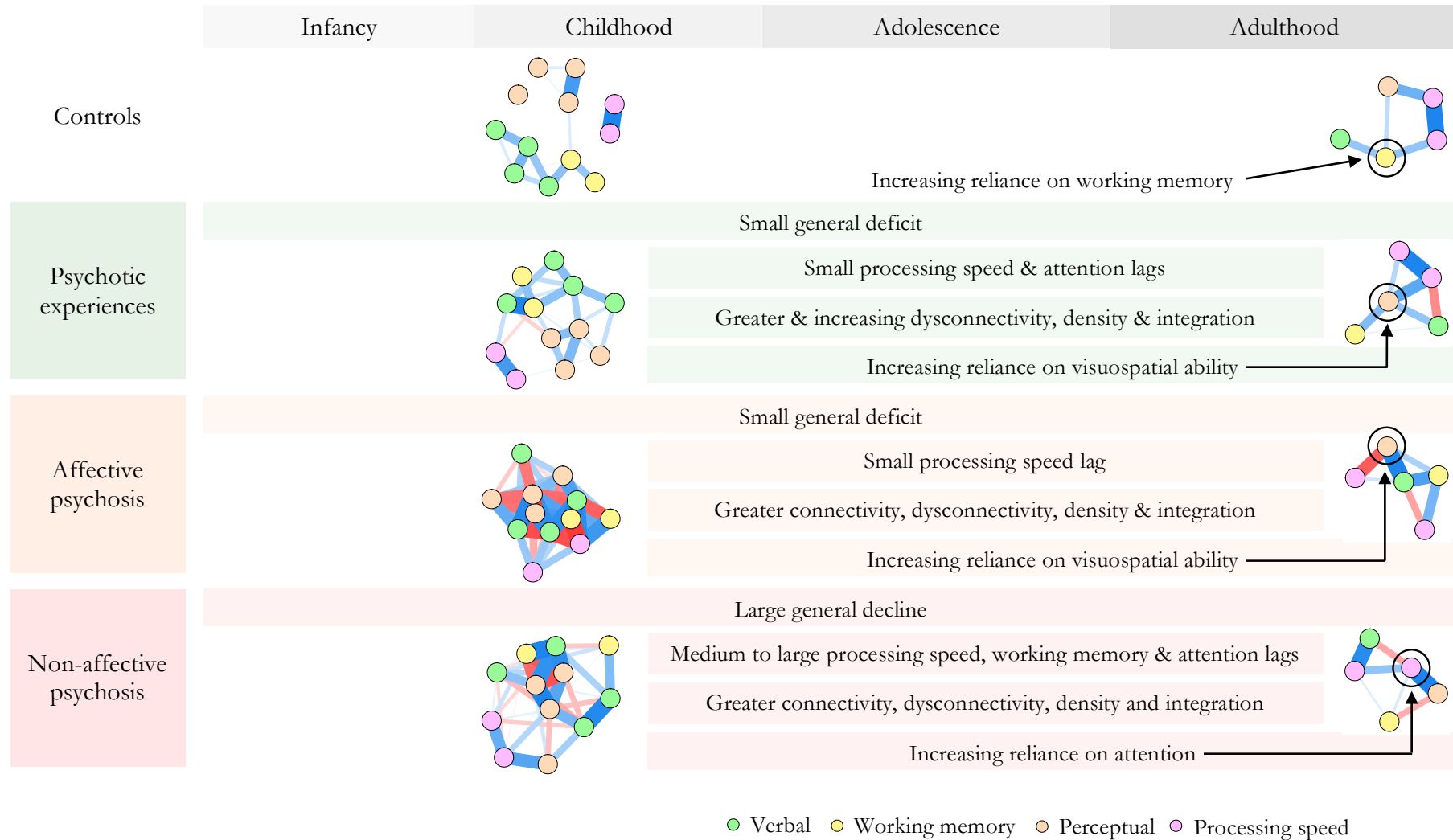
may account for the discrepancy in results regarding processing speed deficits.

Nevertheless, processing speed deficits in individuals with psychotic experiences remained small, which may explain why these individuals had not converted to clinical psychosis. Individuals with affective psychotic disorder showed more substantial lags in processing speed and attention, while the non-affective psychosis group showed large, diffuse, increasing cognitive deficits and lags in processing speed, attention and working memory.

In the last study reduced recruitment of working memory functions, and consequently greater reliance on low-level cognitive functions, was found across the psychosis spectrum. Individuals across the psychosis spectrum also showed greater density and integration of cognitive processes, possibly reflecting compensatory mechanisms.

Indeed, the psychotic experiences and affective psychosis groups showed only small to medium cognitive deficits and no working memory lag. The non-affective psychosis group, on the other hand, showed large, increasing deficits and a substantial working memory lag. While the non-affective psychosis also showed greater network density and integration overall, these findings also showed decreasing integration and density between childhood (age 8) and adulthood (age 20) in this group, although these did not reach statistical significance. Nevertheless, these deviations in cognitive network structure from, not only controls, but also individuals with subclinical and affective psychosis, may begin to explain the more severe profile of cognitive deficits seen in individuals with non-affective psychosis.

Figure 5.1 Findings from the ALSPAC cohort on cognitive performance and network structure in early life across the psychosis spectrum



Integration of findings with previous research

Using a large, heterogeneous, representative sample drawn from an urban community (the South East London Community Health study) I replicated findings from the National Survey of Psychiatric Morbidity in Great Britain (Johns et al., 2004), of small cognitive deficits in adults with psychotic experiences. Adjusted effect sizes of specific deficits in our sample (**Table 2.2**) closely approximated pooled effect sizes from the meta-analytic summary, with the exception of the processing speed domain (**Table 2.1**). However, these findings are not directly comparable to those of previous studies, which used younger (Niarchou et al., 2013; Kelleher et al., 2012a; Gur et al., 2014) and older (Henderson et al., 1998; Ostling et al., 2004) samples. Thus, the association between processing speed deficits and psychotic experiences may differ with age. The current findings corroborate those of a recent study, which found no significant difference in processing speed performance between adults with low and high levels of psychotic experiences (Korponay et al., 2014). Moreover, a weak association between subclinical psychosis and processing speed is in line with results of increasing processing speed deficits in clinical psychosis (Reichenberg et al., 2010).

Using a population-based cohort followed prospectively from birth (the Avon Longitudinal Study of Parents and Children), I replicated findings from the longitudinal Dunedin Multidisciplinary Health and Development Study (Reichenberg et al., 2010) of dynamic and static cognitive deficits preceding adult psychotic illness. Results from the second study showed that individuals who later developed non-affective psychotic disorder demonstrated increasing processing speed, working memory and attention deficits during the developmental period encompassing adolescence. Language and

visuospatial deficits, on the other hand, remained relatively stable during this time. In line with longitudinal findings from Dunedin (Reichenberg et al., 2010; Meier et al., 2013) and Sweden (MacCabe et al., 2013), individuals who later developed non-affective psychotic disorder also showed evidence of IQ decline.

Results of the second study extended previous findings by providing evidence that individuals with non-affective psychosis showed normal IQ performance in infancy, followed by IQ decline through childhood, adolescence and early adulthood (Reichenberg et al., 2010; Meier et al., 2013; MacCabe et al., 2013). The majority of the decline in verbal IQ occurred during early childhood, which may account for contrasting findings of static verbal deficits in late childhood and between adolescence and middle adulthood in the Dunedin study (Reichenberg et al., 2010; Meier et al., 2013). Individuals who later developed non-affective psychotic disorder showed further decline in verbal IQ during adolescence, albeit of smaller magnitude than in the Swedish longitudinal cohort (MacCabe et al., 2013). This cohort, however, consisted only of male conscripts, limiting the generalizability of findings and perhaps accounting for the larger decline in verbal IQ (Albus et al., 1997; Goldstein et al., 1998; Hoff et al., 1998). The magnitude of deficits in early adulthood matched that of schizophrenia patients, in line with cross-sectional evidence that cognitive decline begins many years before the onset of psychotic disorder and peaks around the first stages of illness (Mesholam-Gately et al., 2009; Heinrichs and Zakzanis, 1998).

Finally, individuals who later developed psychotic disorders showed aberrant connectivity and organization of cognitive processes in childhood (age 8), in line with conceptualization of schizophrenia as a disorder of brain dysconnectivity (Friston and

Frith, 1995). Individuals with affective and non-affective psychotic disorder showed gross disorganization of cognitive functions and disruption to cognitive hubs, lending support to the hubopathy hypothesis (Rubinov and Bullmore, 2013), which posits that schizophrenia is characterized by abnormalities in brain hubs. Affective and non-affective psychosis groups also showed greater network connectivity, dysconnectivity, integration and density than controls. These findings are in line with previous factor analytic and imaging studies, which have found stronger associations between cognitive processes (Dickinson et al., 2006; Haring et al., 2015; Strauss and Summerfelt, 2003), as well as increased clustering within brain regions (van den Heuvel et al., 2010; Bassett et al., 2008) and shorter path lengths (Rubinov et al., 2009). Greater network integration and density were also seen in individuals with psychotic experiences, suggesting that alterations in network connectivity, integration and density may extend, not only to affective psychotic disorder, but also to subclinical psychosis. The current findings corroborate previous findings of topological brain abnormalities in individuals with subclinical psychotic experiences in the ALSPAC sample (Drakesmith et al., 2015).

Between childhood (age 8) and adulthood (age 20), controls showed increased reliance on working memory functions, in line with evidence that executive functions mature relatively late in development (Casey et al., 2005). Individuals with psychotic experiences, affective and non-affective psychotic disorders, on the other hand, remained more reliant on low-level cognitive processes, such as attention and visuospatial ability. These findings are in line with previous evidence of increased reliance on low-level cognitive processes in schizophrenia patients during digit symbol coding test performance (Knowles et al., 2015). The results of the third study extended these findings by providing evidence that normal development of higher cognitive

functions may be delayed or even absent in young people with non-affective, but also affective psychotic disorders, as well as subclinical psychotic experiences.

Implications

These findings have important theoretical and clinical implications. First, a substantial minority (9.7%) of adults in the general population sample reported psychotic experiences, which were associated with cognitive deficits across verbal, working memory and working memory functions. While the effect sizes reported were small, cognitive remediation efforts could have significant and even life-changing consequences for many individuals (Gur, 2015). Moreover, cognitive deficits in older adults with psychotic experiences were larger and more robust, suggesting that psychotic experiences in later life may indicate vulnerability to accelerated cognitive aging. Theoretically, these findings highlight differences in cognitive impairment associated with psychotic experiences through adulthood, which may reflect age dependent pathways (**Appendix I, eFigure 5**).

Moreover, these findings suggest that the cognitive deficits associated with non-affective psychotic disorder may be due to a single, dynamic process across cognitive functions. Importantly, observed cognitive decline may be due to a failure to keep up with developmentally normal rates of cognitive growth, rather than an absolute loss or deterioration in cognition over time. Crystallized abilities may decline during infancy and remain relatively stable thereafter, while deficits in fluid abilities may increase monotonically throughout childhood, adolescence and early adulthood. Thus, crystallized abilities may be more amenable to cognitive remediation efforts during

childhood, while later interventions, possibly during adolescence, may be most effective for fluid abilities.

These findings also suggest the importance of looking beyond cognitive performance as a risk factor for psychosis. We found aberrant connectivity and organization of cognitive functions across the psychosis spectrum even in the absence of performance deficits. Individuals who developed non-affective psychotic disorder showed gross disorganization and dysconnectivity of cognitive processes, which is in line with results showing large, increasing cognitive deficits in this group. However, the affective psychotic disorder group showed similar aberrations in cognitive network structure despite showing much milder cognitive deficits across limited functions. Individuals with psychotic experiences showed more subtle deviations in cognitive network structure in the absence of diffuse cognitive impairment. These findings suggest the importance of considering, not only cognitive performance, but also how performance is achieved in prediction and early intervention efforts. Our findings of increasing integration and density in cognitive networks between childhood (age 8) and adulthood (age 20) in individuals with affective psychotic disorder and psychotic experiences suggest possible implementation of compensatory mechanisms, which may account for the lack of substantial and increasing cognitive impairment in these groups. These potentially compensatory mechanisms may prove useful in cognitive remediation.

Strengths and limitations

The first study is the first to use a large, heterogeneous, representative sample drawn from an urban community to investigate the effect of age and familial factors on the

association between psychotic experiences and neuropsychological functioning while adjusting for important confounders. Second, I examined the course of full-scale, performance and verbal IQ from infancy (age 18 months), through childhood (age 8) and adolescence (age 15) to early adulthood (age 20) across the psychosis phenotype in a well characterized, epidemiologically sampled, population representative longitudinal study. It was also possible to test directly for cognitive decline during a crucial developmental phase by focussing on the period encompassing adolescence (from age 8 to 20) and using identical measures of general and specific neuropsychological functions across ages. Finally, the network structure of cognition across the psychosis spectrum was comprehensively examined in childhood (age 8), as were changes in network structure between childhood (age 8) and adulthood (age 20).

Nevertheless, a number of limitations warrant consideration. First, cross-sectional data were used in the first study and consequently it is not possible to make strong inferences about age-associated effects or conclude that psychotic experiences lead to cognitive deficits. Another plausible explanation is that psychotic experiences and neuropsychological functioning are manifestations of common underlying processes (Toulopoulou et al., 2007; Fowler et al., 2012). Moreover, the timing and history of psychotic experiences could not be established, meaning that some psychotic experiences may be longstanding. Future longitudinal studies that are able to disentangle the temporal sequence of psychotic experiences and cognitive deficits and to determine whether our findings also apply to lifetime psychotic experiences are needed.

In the second study, imputation methods were used to analyse data spanning from infancy to adulthood since small numbers of individuals with affective and non-affective psychotic disorder were available in infancy (18 months) and early childhood (age 4). Thus, these results require replication in other well-characterised, population-based, longitudinal cohorts. Moreover, in this and the last study, only five cognitive subtests were available for longitudinal analyses of changes in cognitive functioning and cognitive network structure between childhood (age 8) and adulthood (age 20). Future longitudinal studies, which include additional tests of complex reasoning and social cognition, as well as brain imaging, could help elucidate pathophysiological pathways to disease and suggest targets for intervention.

Future directions

These findings suggest that subclinical psychotic experiences are associated with varying degrees of cognitive impairment throughout the lifespan. The magnitude of impairment also differed between individual psychotic experiences, with hallucinations showing the strongest association with verbal and memory deficits (**Appendix 1, eTable 5**). Hallucinations have been hypothesized to precede and even precipitate development of delusions, which may arise as an attempt to explain repeated anomalous experiences (Maher, 2006). Nevertheless, certain patients with psychosis experience delusions in isolation from hallucinations and evidence suggests that these individuals show better symptomology, as well as social and occupational functioning (Compton et al., 2012). In the first study, paranoia showed the weakest association with cognitive deficits, while hallucinations showed the strongest (**Appendix 1, eTable 5**). Future longitudinal research into the emergence of individual psychotic symptoms and

their cognitive correlates in the general population, but also in those who go on to develop clinical psychotic disorders, could provide important clues about the etiology of psychosis and associated cognitive impairment.

The current findings showed that individuals with affective psychotic disorder outperformed the non-affective psychosis group across all cognitive functions, suggesting that psychotic disorders with and without affective features may have different etiologies (Murray et al., 2004). While common genes may increase susceptibility to affective and non-affective psychosis (Purcell et al., 2009), distinct neurodevelopmental profiles suggest additional genetic and/or environmental risk factors (Murray et al., 2004). Future investigations examining whether environmental stressors predispose more to affective psychosis accompanied by mild cognitive deficits, while early neurodevelopmental insults predispose more to non-affective psychosis accompanied by severe impairment, are needed.

Conclusions

The profile of cognitive impairment in individuals with psychotic experiences differed by age and from that found in psychotic disorders. Young people with psychotic experiences showed small, general deficits while older adults showed large memory deficits. The course of deficits also differed between subclinical and clinical psychosis, as well as between affective and non-affective psychotic disorders. Large, increasing deficits across functions were specific to the non-affective psychosis group. The affective psychosis and psychotic experiences groups showed small, mostly stable deficits. The network structure of cognitive functioning in individuals with affective

and non-affective psychosis showed gross organization and connectivity abnormalities. Individuals with psychotic experiences showed more subtle deviations in network integration and density. Deviations in cognitive network structure occurred in affective psychosis and psychotic experiences groups despite normal cognitive performance. Altogether, these findings provide evidence that the course of cognitive deficits differs across the psychosis spectrum and highlight the importance of looking beyond performance to how performance is attained.

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Appendix

I. Online Supplemental Material

The materials presented herein were published as supplemental materials in the JAMA Psychiatry manuscript:

eMethods Summary of meta-analysis

eFigure 1 Flow chart representing the number of published papers selected and excluded from the database searches through to the publications included in the review

eTable 1 Psychosis Screening Questionnaire items and responses

eTable 2 Neuropsychological battery

eTable 3 Correlation matrix of all variables

eTable 4 Characteristics of participants by psychotic experiences group

eTable 5 Group means and effect sizes (Cohen *d*) by psychotic experience

eFigure 2 Sensitivity analysis: Effect sizes for each neuropsychological test by age group before and after adjusting for confounders

eTable 6 Effect sizes after for each neuropsychological test adjusting for confounders plus educational level

eFigure 3 Effect sizes for each neuropsychological test by age group after adjusting for confounders plus educational level

eTable 7 Sample characteristics by familial group

eFigure 4 Local regression curves of neuropsychological tests on age by familial group

eFigure 5 Hypothesized model of the etiology of neuropsychological impairments associated with psychotic experiences through adulthood

eMethods Summary of meta-analysis

Literature Search

The meta-analysis was conducted according to the PRISMA guidelines. Studies were identified by searching electronic databases PubMed and PsycInfo using the following search terms: ‘psychotic symptoms’ or ‘attenuated psychotic symptoms’ or ‘psychotic like experiences’ or ‘psychotic experiences’ and ‘cognition’ or ‘neuropsychology’ or ‘IQ’ or ‘neurocognition’. Papers published between 1980 and 1st December 2014, when the search was run, in the English language and using human subjects were included. The aim was to identify population based epidemiological studies in order to minimise bias and increase generalizability. A total of 2487 papers were identified initially through the literature search and after reviewing all titles and abstracts 14 were identified as potentially relevant. The reference lists of these 14 studies were hand searched for potentially relevant studies and two further articles were identified: giving a total of 16 potentially relevant studies.

Eligibility Criteria

Inclusion criteria comprised: population based sample of subjects with subclinical psychotic symptoms; comparison subjects drawn from the same population; valid and reliable measure of subclinical psychotic symptoms; valid neuropsychological measure(s); sample of at least 100 participants. Exclusion criteria were: patients with psychotic illness or with an at risk mental state (ARMS). The inclusion and exclusion criteria were used in order to ensure that all included studies were relevant, valid and produced reliable results. All 16 studies identified through the literature search were reviewed using the eligibility criteria. **eFigure 1** represents the number of published

papers selected and excluded from the database searches through to the publications included in the review.

Data Extraction

Key data elements extracted were author and year of publication, sample size, measures used and outcomes of interest.

Primary outcomes

Neuropsychological functioning outcomes measured using various scales, for example: the Stanford Binet test of IQ, subtests of the Wechsler Intelligence Scale for Children (WISC) and the National Adult Reading Test (NART). The cognitive domains of interest were: general cognitive ability, IQ, processing speed, working memory and memory.

Statistical analysis

All analyses were conducted in STATA software (version 14; Stata-Corp) and the Comprehensive Meta-Analysis Software Version 3. Effect sizes for each study were calculated using Cohen *d* standardized mean differences. A single mean effect size was calculated for studies with multiple measures of the same cognitive domain. Sample weighted mean effect sizes were then calculated for each cognitive domain: IQ, general cognition, processing speed, working memory and memory.

Results

In our literature search, we identified 14 studies that reported neuropsychological performance in subjects with and without psychotic experiences. Of these, two were excluded because of small ($N < 100$) sample size, two because they did not use a valid

neuropsychological measure and one because it did not use a valid measure of psychotic experiences. **Table 2.1** details basic study characteristics and mean effect sizes for the 11 studies included in our analyses.

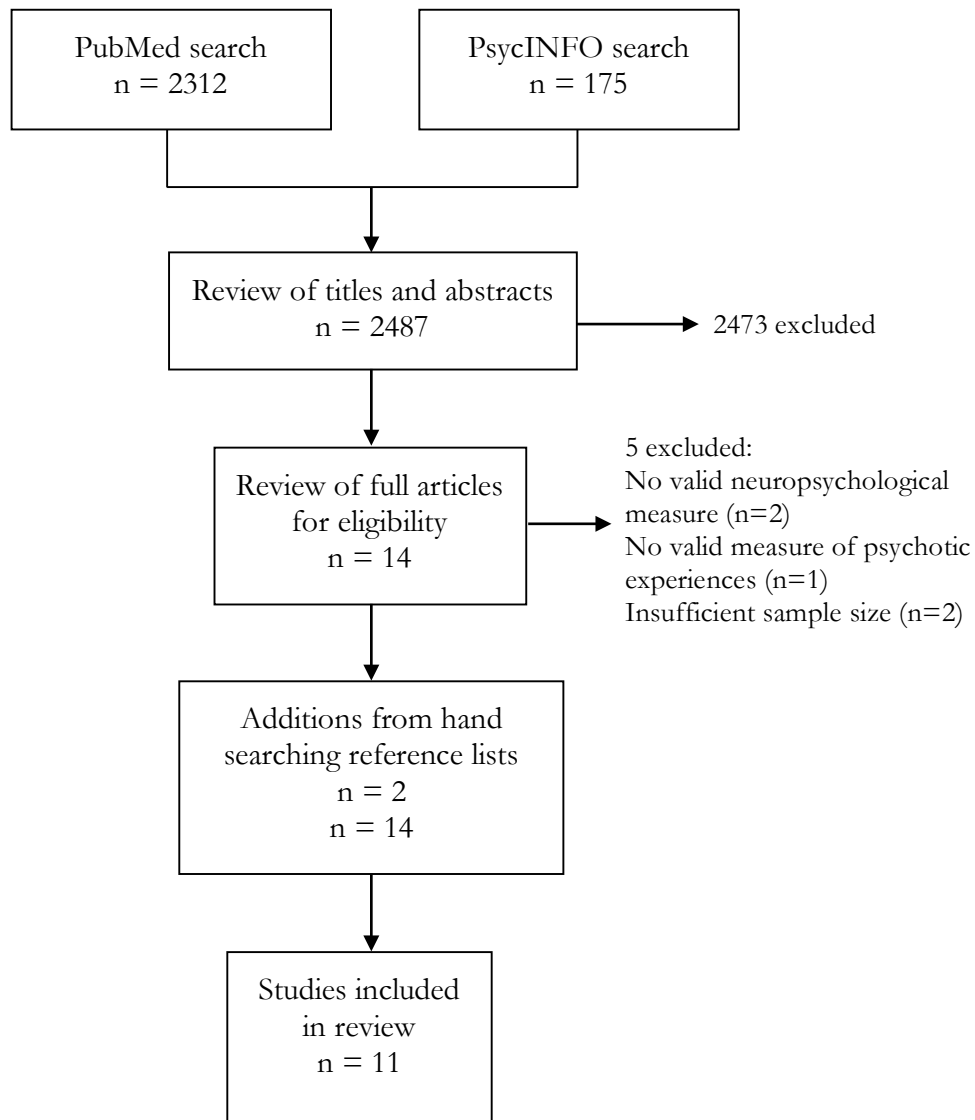
Mean Effect Sizes by Neuropsychological Domain

The pooled effect size for studies measuring IQ included in our analyses was: Cohen $d=-0.40$, suggesting a medium-sized deficit in IQ in those with subclinical psychotic experiences. Effect sizes for the specific domains included in our analyses were smaller, with memory being the most impaired (Cohen $d=-0.31$), followed by processing speed (Cohen $d=-0.20$), general cognition (Cohen $d=-0.19$) and working memory (Cohen $d=-0.18$).

Discussion

To our knowledge, this is the first quantitative review of the literature on neuropsychological functioning (IQ, general cognition, working memory, processing speed and memory) in people with subclinical psychotic experiences. Our findings suggest a medium IQ deficit and small general cognition, working memory, memory and processing speed impairments in those reporting psychotic experiences. Psychotic experiences may therefore be a subclinical phenotype of schizophrenia, with a similar, but milder profile of neuropsychological impairment. Our findings also highlight the need for further investigation into the neuropsychological correlates of psychotic experiences since the studies to date have mostly focussed on child/adolescent samples and were unable to control for important demographic and psychosocial confounders.

eFigure 1 Flow chart representing the number of published papers selected and excluded from the database searches through to the publications included in the review



eTable 1 Psychosis Screening Questionnaire items and responses

PSQ items	Yes responses	
	n	%
Initial probe		
Secondary question		
Secondary question (highest level)		
Thought insertion		
Over the past year, have you ever felt that your thoughts were directly interfered with or controlled by some outside force or person?	125	7.2
Did this come about in a way that many people would find hard to believe, for instance, through telepathy?	19	1.1
Paranoia		
Over the past year, have there been times when you felt that people were against you?	369	20.9
Have there been times when you felt that people were deliberately acting to harm you or your interests?	218	12.3
Have there been times when you felt that a group of people were plotting to cause you serious harm or injury?	53	2.9
Strange experiences		
Over the past year, have there been times when you felt that something strange was going on?	264	14.9
Did you feel it was so strange that other people would find it very hard to believe?	96	5.5
Hallucinations		
Over the past year, have there been times when you heard or saw things that other people couldn't?	123	7.2
Did you at any time hear voices saying quite a few words or sentences when there was no one around that might account for it?	62	3.8
Any psychotic symptom		
Yes to one or more probe questions	552	68.5
Yes to one or more secondary questions	313	17.8
Yes to one or more secondary questions at the highest level	171	9.7

eTable 2 Neuropsychological battery

General cognitive ability composite score (IQ)	The first principal-component of a factor-analysis utilizing all the neuropsychological tests listed below. Scores were transformed to an IQ-like score with mean 100 and standard deviation 15.
Wechsler Test of Adult Reading (WTAR)(Wechsler, 2001)	Used as a measure of general verbal knowledge and is a word reading test that involves pronouncing 50 irregularly spelled words. The 50 words were presented on a page and subjects were asked to read each word aloud. The test was untimed and the dependent variable presented here was the number of correctly pronounced words.
Spatial Delayed-Response Task (SDRT)(Glahn et al., 2003)	Used to measure spatial working memory. During the SDRT, subjects were shown a target array of 3 or 5 yellow circles positioned around a central fixation. After a fixed delay, subjects were shown a single green circle and required to indicate whether that circle was in the same position as one of the target circles. Trial events included a 2 second target-array presentation, a 3 second delay period, and a 3 second fixed response interval. A central fixation was visible throughout each of the 24 trials (12 per memory set size).
Visual Object Learning Task (VOLT)(Glahn et al., 1997)	Used to measure visual memory and comprised four trials. The first 3 were learning trials, in which participants were presented with a set of 10 visual objects and then, in a forced-choice paradigm, required to recognize those stimuli within a group of 20 shapes (10 targets and 10 foils). Each stimulus in the learning set was presented for 5 seconds and recognition trials were self-paced. The composition and order of presentation of the learning set was identical in the three learning trials, but the foils were novel in each trial. The forth trial was about 20 minutes later and was a long-delay recognition condition. Test stimuli were computer-generated three-dimensional Euclidean shapes that were judged to be difficult to verbalize. Number correct during Learning and Delayed recognition were used as the primary dependent measures.
Computerised Digit Symbol Coding Task (DSCT)(Tulsky et al., 1997; Glahn et al., 2010)	Used to measure processing speed. Similar to paper versions of the task, subjects were required to indicate, by pressing a button, if a centrally presented digit-symbol pair was identical to one of the nine digit-symbol pairs in the reference list at the top of the screen(Bachman et al., 2010). Trials were self-paced, but participants were encouraged to work as quickly as possible. The test took four minutes on average to complete and feedback was not provided. The number of correctly identified pairs in 90 seconds was used as the dependent measure in order to obtain scores similar to those from time limited paper versions of the task. Performance on this computerized version of the digit symbol task is highly correlated with pen and paper versions(Tulsky et al., 1997). The between task correlation was $r^2=0.87$ in 30 healthy comparison subjects and $r^2=0.95$ in 85 individuals with schizophrenia(Bachman et al., 2010). While there are differences between the paper and computerized versions of the digit symbol coding, the reduction of the praxic response makes performance on the computerized version putatively more sensitive to processing speed rather than motor ability.

eTable 3 Correlation matrix of all variables

	PEs	IQ	WTAR	SDRT	VOLT	VOLTd	DSCT	Age	Ethnicity	Occupation	Cannabis
IQ	−0.10*										
WTAR	−0.16*	0.48*									
SDRT	−0.12*	0.59*	0.23*								
VOLT	−0.11*	0.87*	0.31*	0.38*							
VOLTd	−0.09	0.79*	0.25*	0.34*	0.61*						
DSCT	−0.04	0.69*	0.32*	0.31*	0.45*	0.38*					
Age	−0.04	−0.34*	0.02	−0.11*	−0.28*	−0.24*	−0.52*				
Ethnicity	0.08*	−0.19*	−0.32*	−0.09*	−0.14*	−0.13*	−0.14*	−0.16*			
Occupation	0.17*	−0.23*	−0.33*	−0.14*	−0.20*	−0.12*	−0.18*	0.08*	0.13*		
Cannabis	0.10*	0.13*	0.06	0.03	0.10*	0.09*	0.17*	−0.25*	−0.07	−0.01	
CMD	0.29*	−0.10*	−0.15*	−0.10*	−0.08	−0.05	−0.07	−0.01	0.01	0.12*	.05

Abbreviations: PEs, psychotic experiences; IQ, intelligence quotient (general composite score); WTAR, Wechsler Test of Adult Reading; SDRT, Spatial Delayed-Response Task; VOLT, Visual Object Learning Task; VOLTd, Visual Object Learning Task delayed; DSCT, Digit Symbol Coding Task; CMD, common mental disorders.

*p<.001

eTable 4 Characteristics of participants by psychotic experiences group*

	Psychotic experiences n=171		Comparison group n=1506		χ^2	<i>p</i>
	n	%	n	%		
Age (years)						
16 to 24	47	13.3	305	86.7		
25 to 34	35	8	368	92.0		
35 to 49	46	9.7	426	90.3		
50 and above	43	8.9	406	91.1	5.12	.163
Ethnicity						
White British	86	7.7	957	92.3		
Other	84	13.2	549	86.8	10.91	.001
Occupational class						
I and II	21	3.8	484	96.2		
III-NM and III-M	21	6.9	254	93.1		
IV and V	18	10.9	146	89.1		
Unclassified	67	11.6	468	88.4		
Unemployed	38	22.1	124	77.9	57.12	<.001
Cannabis use in last year						
No	121	8.4	1258	91.6		
Yes	50	17.1	248	82.9	17.14	<.001
CIS-R score						
0 to 17	104	6.5	1372	93.5		
18 and above	66	33.1	129	66.9	135.38	<.001

Abbreviations: I, professional; II managerial/technical; III-NM, skilled non-manual; III-M, skilled manual; IV, semi-skilled; V, unskilled; CIS-R, Revised Clinical Interview Schedule.

*All percentages are weighted.

eTable 5 Group means and effect sizes (Cohen *d*) by psychotic experience*

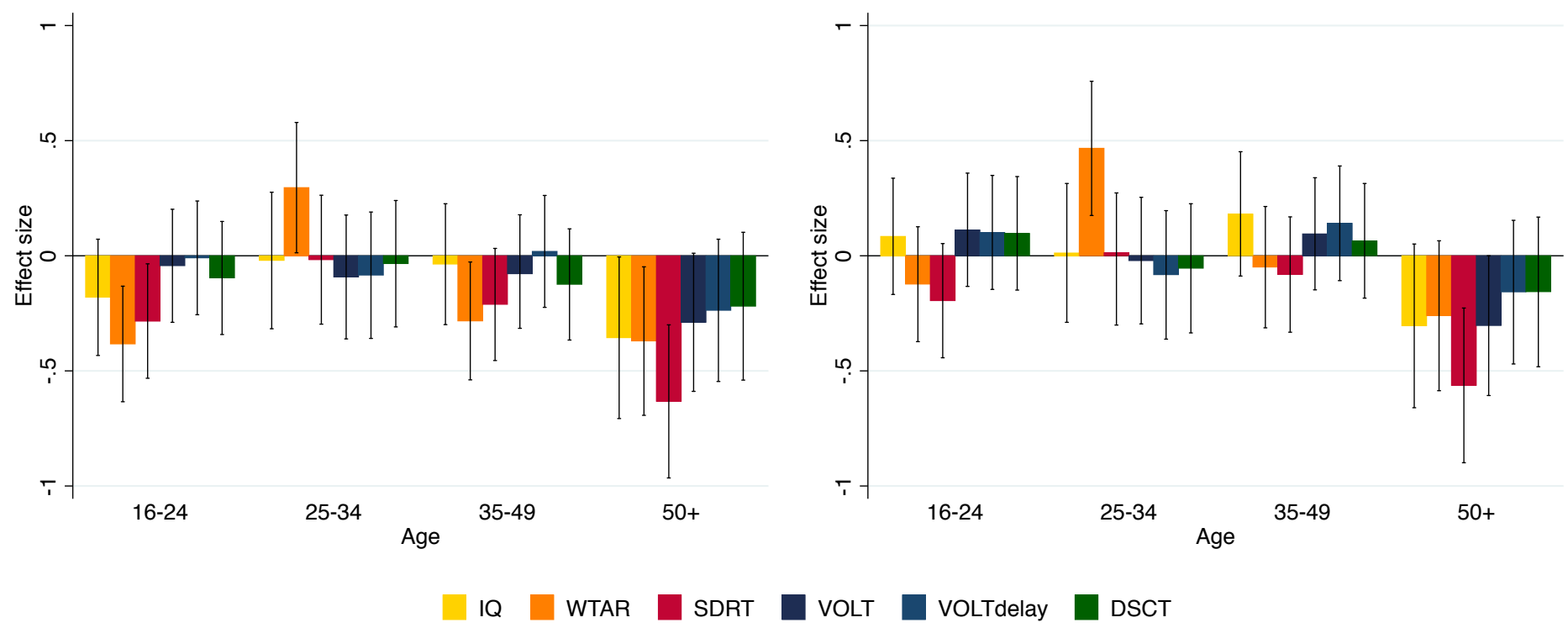
	Controls n= 1,506		Thought insertion n= 19				Paranoia n=53				Strange experiences n=96				Hallucinations n=62			
	Mean	(SD)	Mean	(SD)	Effect size ¹	<i>p</i> ¹	Mean	(SD)	Effect size ¹	<i>p</i> ¹	Mean	(SD)	Effect size ¹	<i>p</i> ¹	Mean	(SD)	Effect size ¹	<i>p</i> ¹
IQ	100.45	(14.77)	91.26	(12.35)	-.28	.2	97.98	(17.37)	.07	.7	94.90	(16.48)	-.25	.1	91.77	(16.89)	-.29	.1
WTAR total	39.06	(10.39)	26.42	(12.78)	-.78	.004	35.08	(13.65)	-.25	.2	33.14	(13.21)	-.37	.02	28.18	(14.87)	-.82	<.001
SDRT total	22.63	(2.88)	20.69	(4.47)	-.43	.2	22.58	(2.71)	.11	.5	21.53	(3.51)	-.30	.06	20.95	(3.67)	-.45	.03
SDRT low load	12.09	(1.70)	11.50	(2.63)	-.15	.7	12.31	(1.72)	.23	.2	11.56	(2.18)	-.25	.1	11.37	(2.19)	-.34	.1
SDRT high load	10.53	(1.67)	9.19	(1.94)	-.60	.03	10.28	(1.47)	-.06	.7	9.97	(1.79)	-.27	.07	9.58	(1.85)	-.44	.02
VOLT total	47.03	(6.02)	43.06	(6.65)	-.42	.1	44.05	(8.11)	-.31	.1	45.16	(7.36)	-.23	.1	43.47	(6.97)	-.37	.03
VOLT delay	15.29	(2.50)	13.75	(2.57)	-.36	.2	14.95	(2.55)	.03	.8	14.51	(2.50)	-.27	.03	14.45	(2.62)	-.21	.2
DSCT	43.46	(11.55)	39.60	(12.49)	-.11	.6	45.19	(12.36)	.28	.05	39.83	(11.53)	-.19	.1	41.20	(11.87)	.01	.9

Abbreviations: WTAR, Wechsler Test of Adult Reading; SDRT, Spatial Delayed Response Task; VOLT, Visual Object Learning Task; DSCT, Digit Symbol Coding Task.

¹Adjusted for ethnicity, occupational status, cannabis use in last year and common mental disorders

*Results in bold signify $p < .05$

eFigure 2 Sensitivity analysis: Effect sizes for each neuropsychological test by age group before (left) and after (right) adjusting for confounders

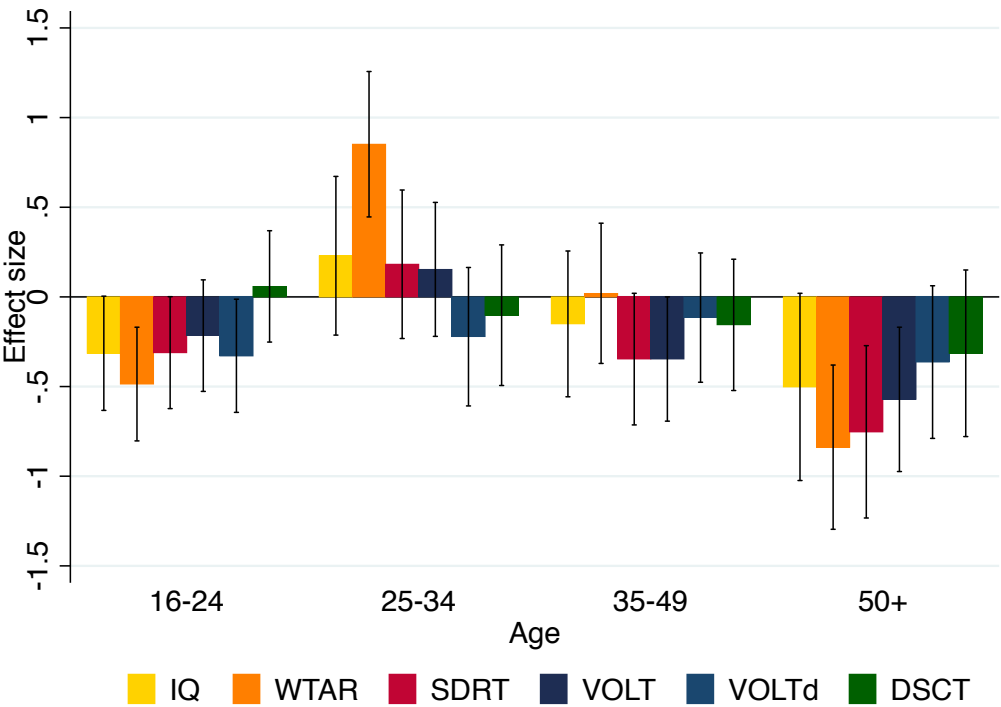


eTable 6 Effect sizes after for each neuropsychological test adjusting for confounders plus educational level

Neuropsychological test	Effect size	95% CIs	
IQ	-.11	-.31	.09
WTAR	-.24	-.43	-.05
SDRT total	-.29	-.48	-.10
SDRT low load	-.22	-.41	-.03
SDRT high load	-.28	-.47	-.09
VOLT total	-.21	-.38	-.03
VOLT delay	-.18	-.36	.01
DSCT	.02	-.16	.21

Abbreviations: WTAR, Wechsler Test of Adult Reading; SDRT, Spatial Delayed Response Task; VOLT, Visual Object Learning Task; DSCT, Digit Symbol Coding Task.

eFigure 3 Effect sizes for each neuropsychological test by age group after adjusting for confounders plus educational level

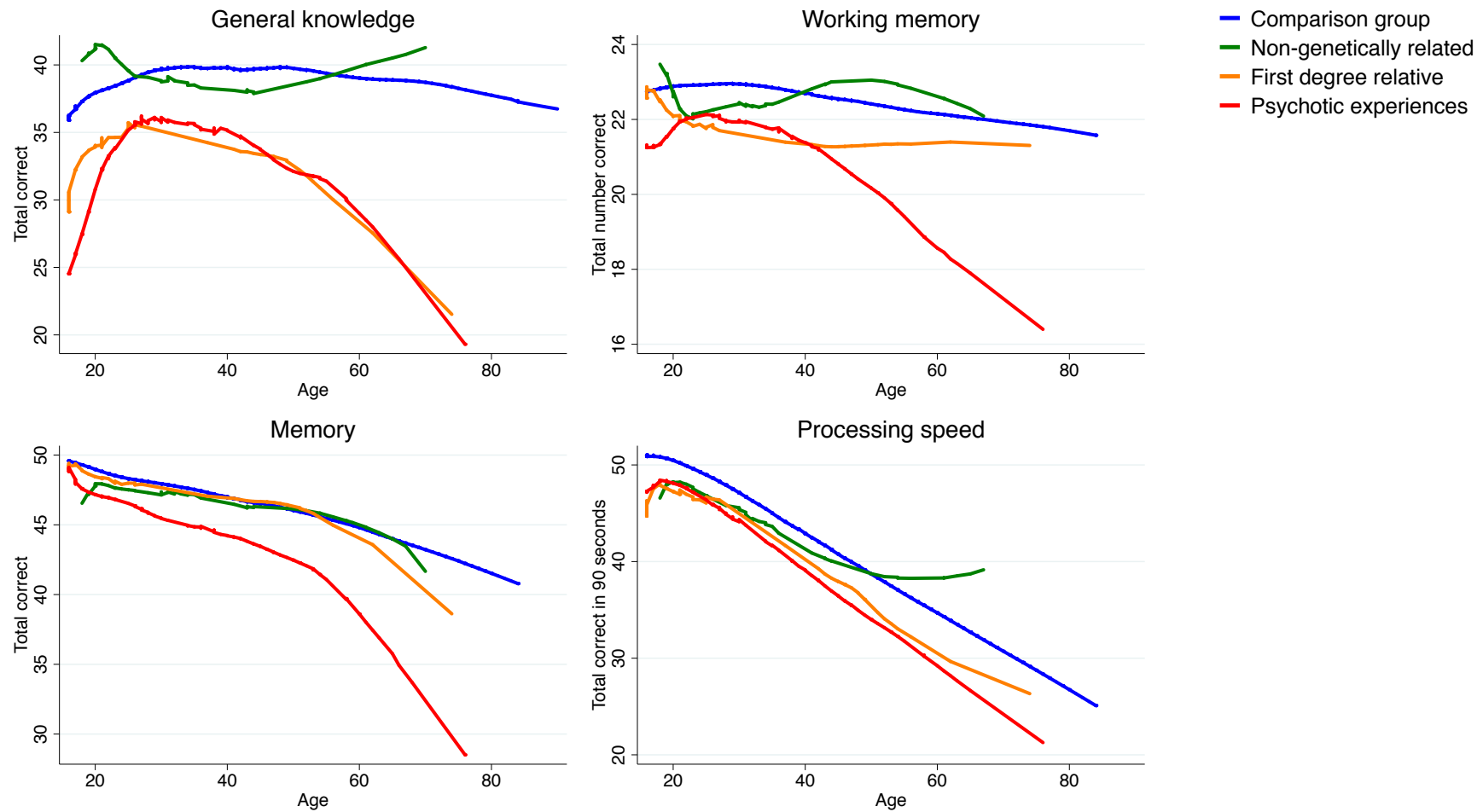


eTable 7 Sample characteristics by familial group

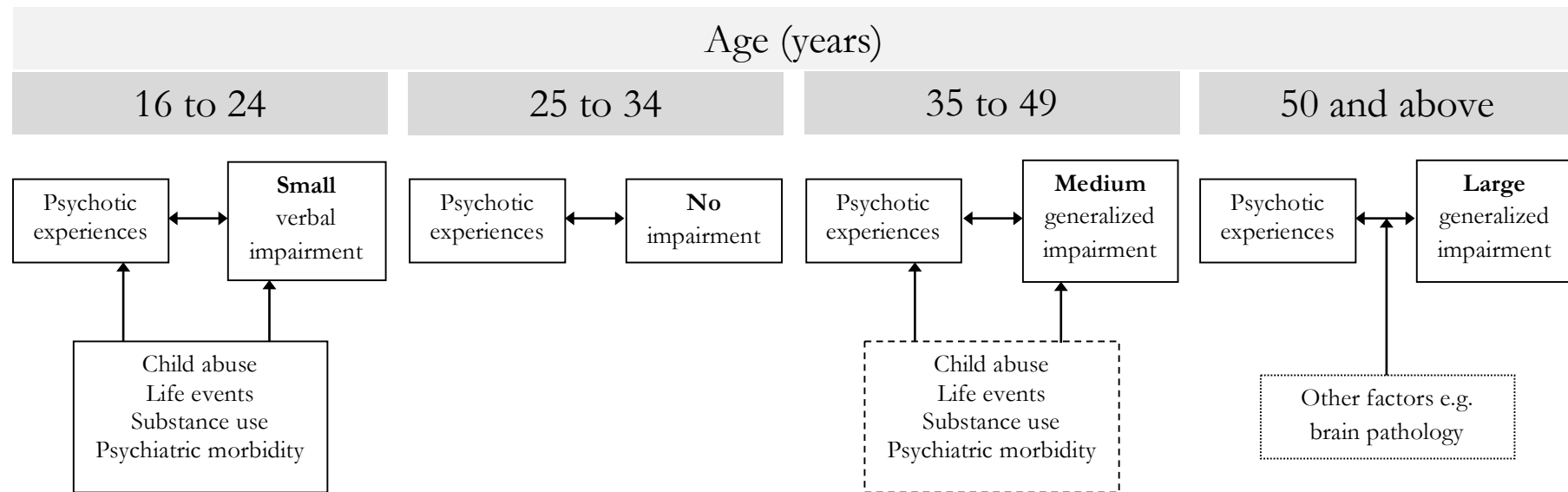
	Comparison group n = 1384		Non-genetically related n = 60		First degree relatives n = 62		Psychotic experiences n = 171	
	n	%	n	%	n	%	n	%
Age (mean, SD)	40.5	17.0	38.5	15.8	33.6	16.6	37.8	16.4
Ethnicity								
White British	891	64.4	38	63.3	28	45.2	86	50.6
Other	493	35.6	22	36.7	34	54.8	84	49.4
Occupational class								
I & II	459	33.8	15	25.4	10	16.4	21	12.7
III	230	17.0	14	23.7	10	16.4	21	12.7
IV & V	130	9.6	8	13.6	8	13.1	18	10.9
Unclassified	430	31.7	17	28.8	21	34.4	67	40.6
Unemployed	107	7.9	5	8.5	12	19.7	38	23.0
Cannabis use								
No	1160	83.8	48	80	50	80.6	121	70.8
Yes	224	16.2	12	20	12	19.4	50	29.2
CIS-R score								
0 to 17	1260	91.3	58	98.3	54	87.1	104	61.2
18 and above	120	8.7	1	1.7	8	12.9	66	38.8

Abbreviations: I, professional; II managerial/technical; III-NM, skilled non-manual; III-M, skilled manual; IV, semi-skilled; V, unskilled; CIS-R, Revised Clinical Interview Schedule.

eFigure 4 Local regression curves of neuropsychological tests on age by familial group



eFigure 5 Hypothesized model of the etiology of neuropsychological impairments associated with psychotic experiences through adulthood*



*In early adulthood the association is confounded by child abuse, stressful life events, substance use and psychiatric morbidity. In mid adulthood the association is partly, but not entirely, confounded by these factors. In late adulthood the large memory deficits associated with psychotic experiences are not attenuated by the confounders we measured and may be due to other factors such as brain pathology.

II. Supplemental material for Chapter 3

Methods Data imputation

Figure 1 Standardized scores at ages 8 and 20 from the high-risk longitudinal sample and at ages 18 months 4, 8, 15 and 20 years from all available individuals

Figure 2 Aggregating affective and non-affective psychosis groups at ages 18 months and 4 years: Standardized scores and effect sizes by group at ages 18 months, 4, 8, 15 and 20 years

Figure 3 Standardized scores and effect sizes by diagnostic group at ages 18 months, 4, 8, 15 and 20 years

Figure 4 Comorbid for depression and psychotic experiences group analyses: Data available at ages 18 months, 4, 8, 15 and 20 years

Figure 5 Comorbid for depression and psychotic experiences group analyses: Standardized scores and effect sizes by diagnostic group at ages 18 months, 4, 8, 15 and 20 years

Figure 6 Comorbid for depression and psychotic experiences group analyses: Flowchart depicting selection of longitudinal high-risk sample

Figure 7 Comorbid for depression and psychotic experiences group analyses: Standardized scores and effect sizes by group at ages 8 and 20 years

Methods

Data imputation

We used imputation analysis with chained equations in STATA software (version 13; Stata-Corp) in order to determine whether the smaller group sizes at ages 18 months and 4 years could lead to bias in the observed associations. Missing data was imputed for full-scale and verbal IQ at ages 18 months and 4 years, and performance IQ at age 4. Twenty-eight measures were included in the imputation model, including cognitive variables at ages 8 and 15, as well as variables relating to parental sociodemographic characteristics, such as parental educational qualifications and house crowding indices. Fifty datasets were imputed.

Figure 1 Standardized scores at ages 8 and 20 from the high-risk longitudinal sample and at ages 18 months 4, 8, 15 and 20 years from all available individuals

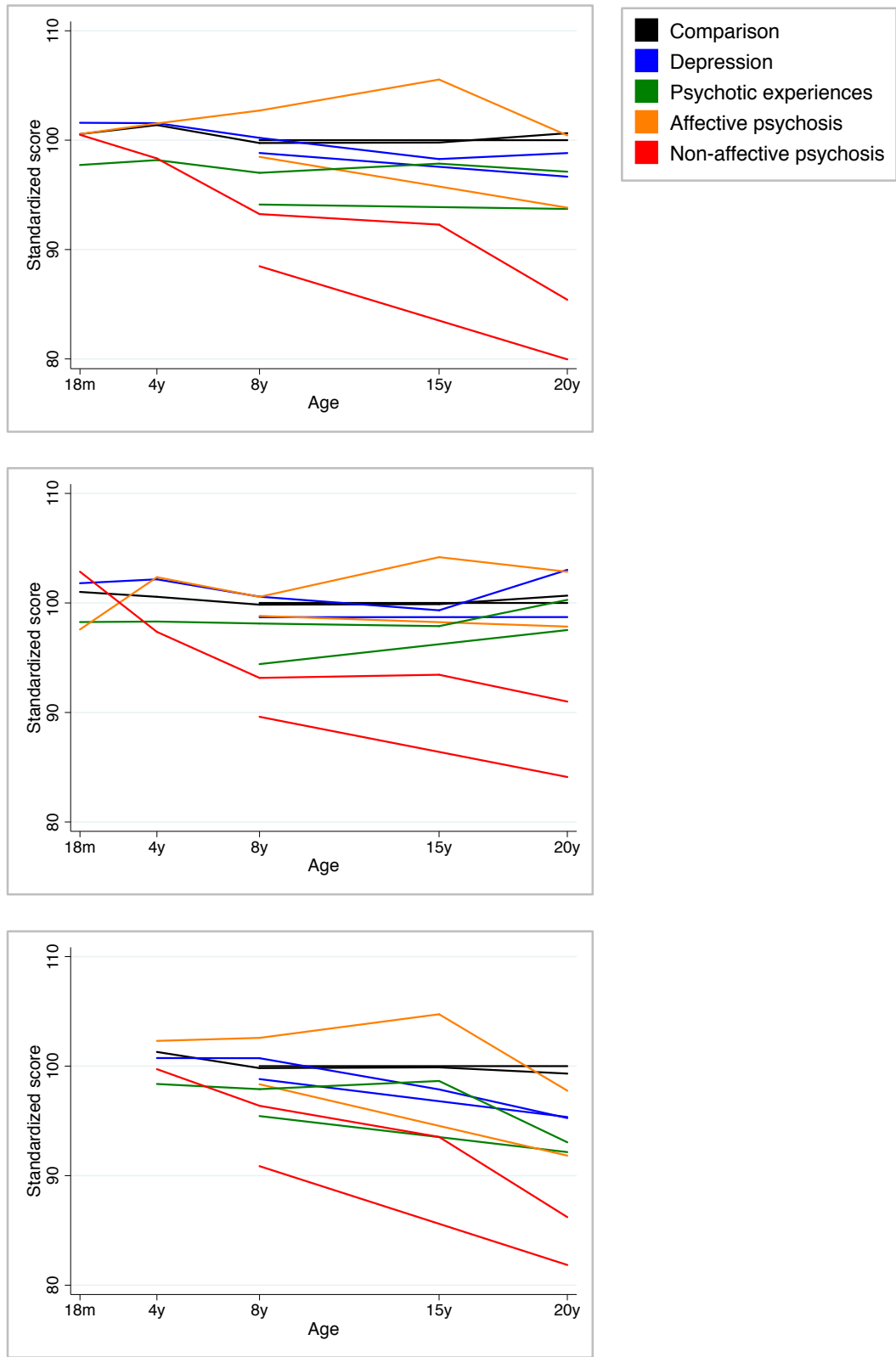


Figure 2 Aggregating affective and non-affective psychosis groups at ages 18 months and 4 years: Standardized scores and effect sizes by group at ages 18 months, 4, 8, 15 and 20 years

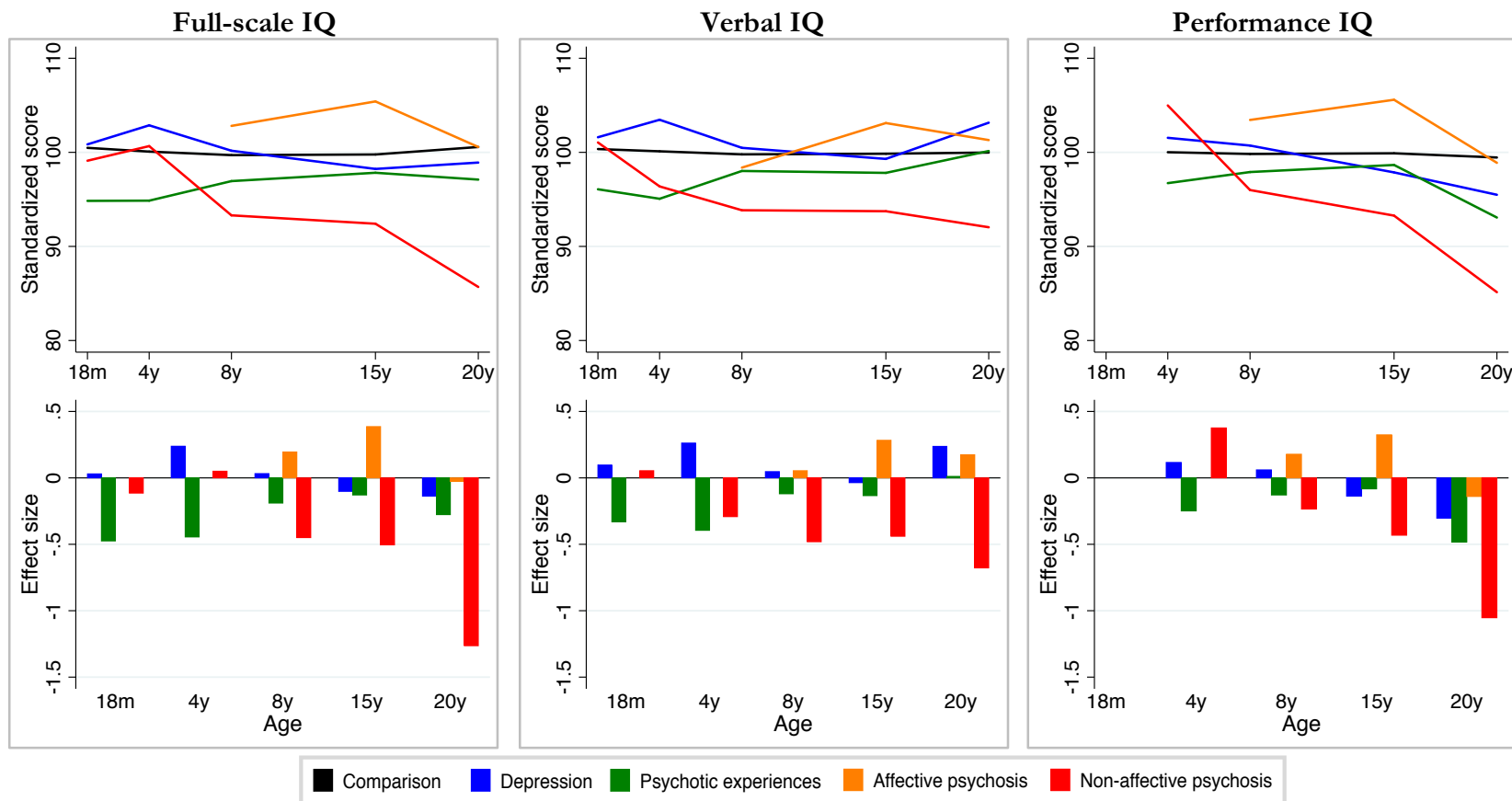


Figure 3 Standardized scores and effect sizes by diagnostic group at ages 18 months, 4, 8, 15 and 20 years

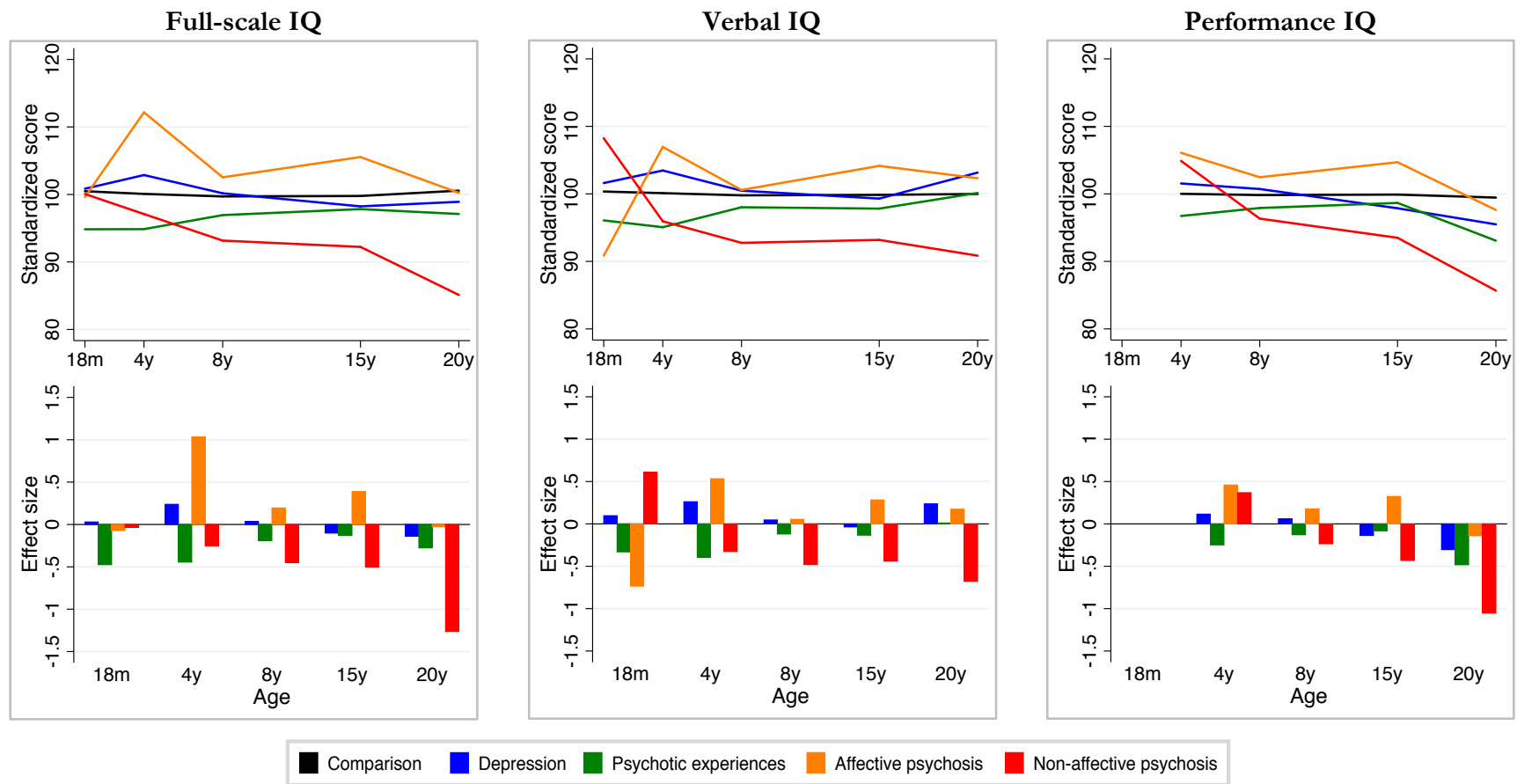


Figure 4 Comorbid for depression and psychotic experiences group analyses: Data available at ages 18 months, 4, 8, 15 and 20 years

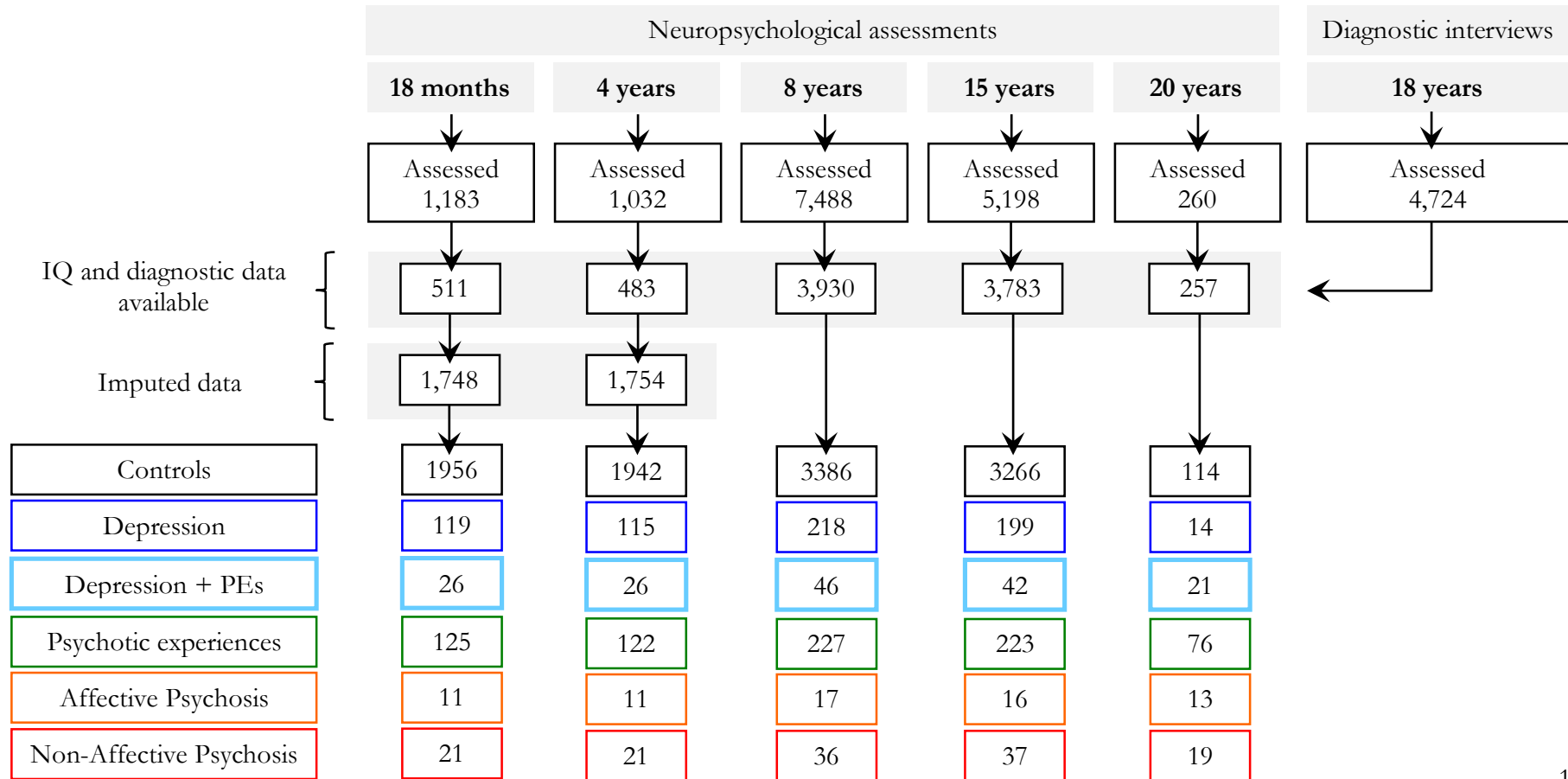


Figure 5 Comorbid for depression and psychotic experiences group analyses: Standardized scores and effect sizes by diagnostic group at ages 18 months, 4, 8, 15 and 20 years

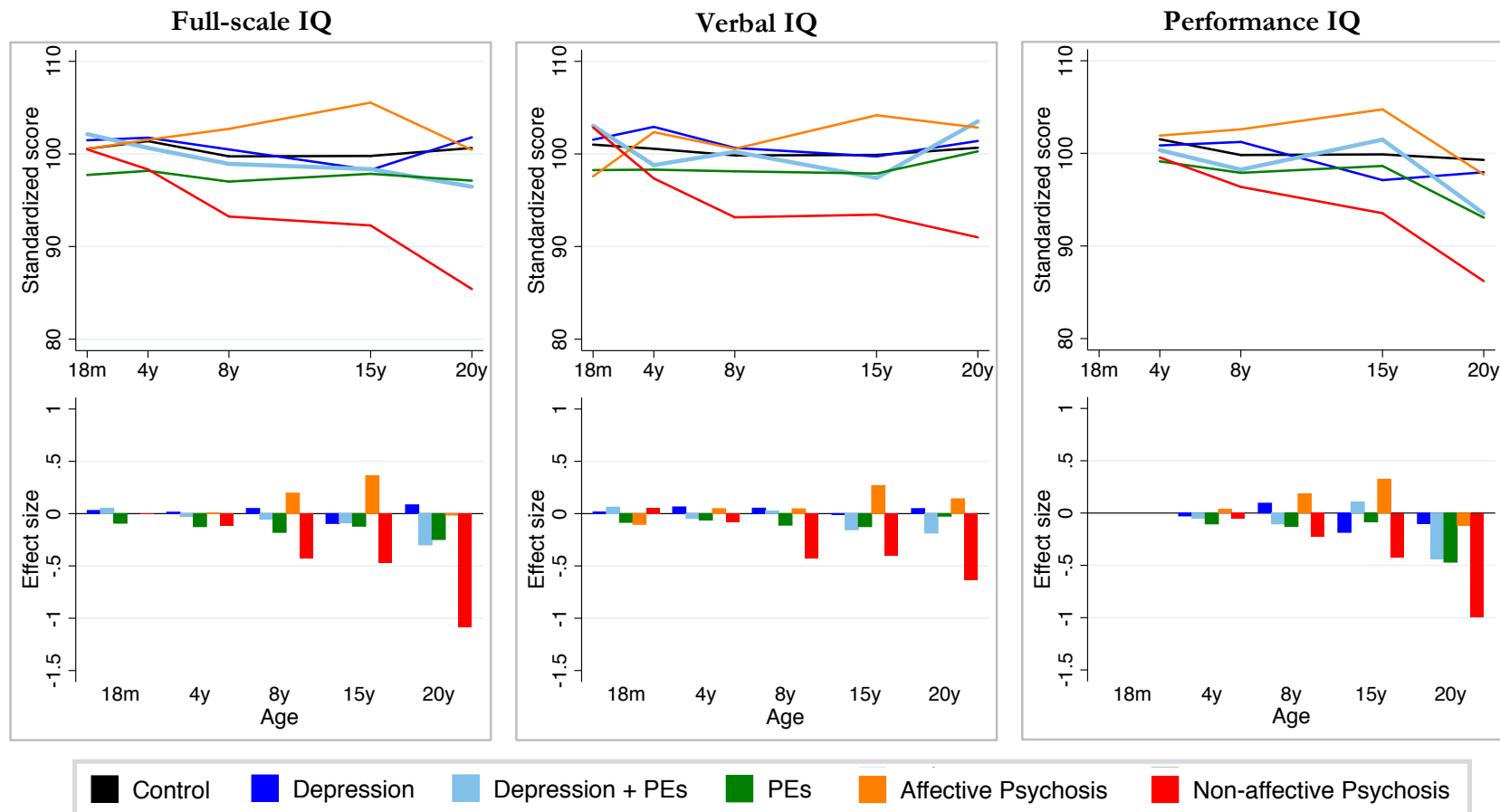


Figure 6 Comorbid for depression and psychotic experiences group analyses:

Flowchart depicting selection of longitudinal high-risk sample

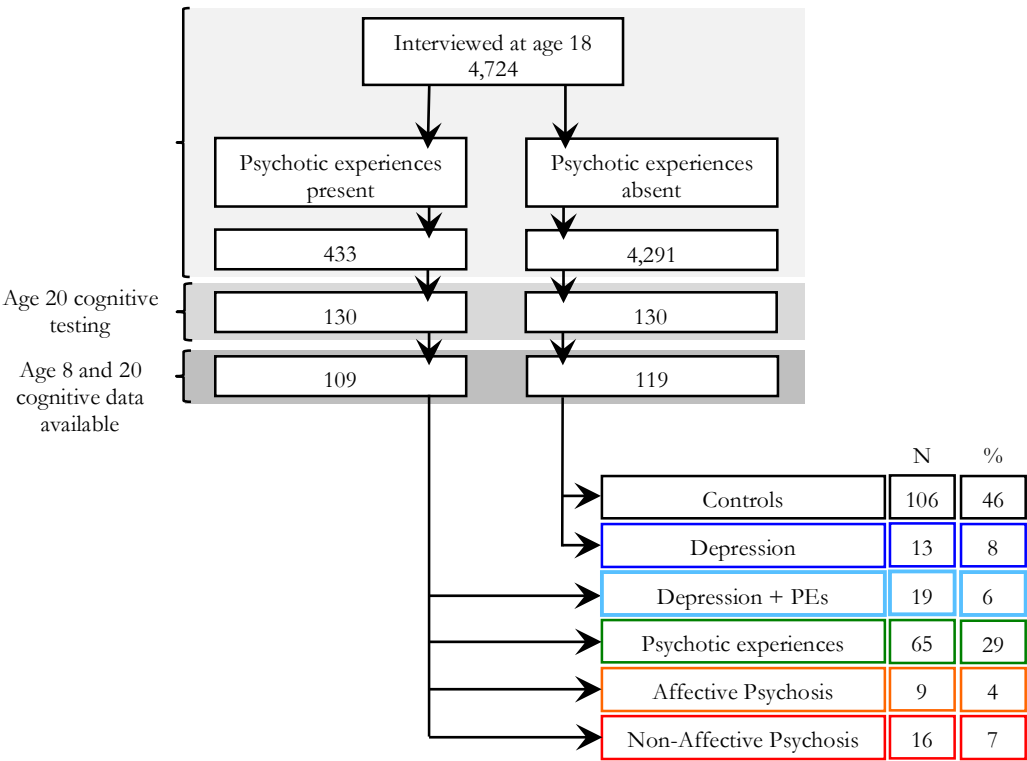


Figure 7 (continued) Comorbid for depression and psychotic experiences group analyses: Standardized scores and effect sizes by group at ages 8 and 20 years

